Tumors of the Soft Somatic Tissues

A CLINICAL TREATISE

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WITH 652 ILLUSTRATIONS



A HOEBER-HARPER BOOK

Acknowledgments

No monographic treatise can ignore the many previous contributions to the subject by the labors and ideas of earlier workers In this light, one remembers the reply of Lord Moynihan to praise for a speech he had just delivered "I have gathered a posie of other mens flowers and nothing but the thread that binds them is mine own" Our acknowledgments to our predecessors are best annotated in the selected bibliography that accompanies each chapter

A complete review of the literature on any medical topic, with critical analysis and summarical presentation, has value as a compendium of information, but only too often it lacks the perspective of original thought and experience Most of the chapters in this book present original experience and some were written with the collaboration of doctors who were or are now associated with the authors The names of these collaborators are listed facing the title page To each and all of them we express our appreciation for their interest and assistance

Dr Gordon McNeer and the late Dr Isabel Scharnagel senior colleagues on the Mixed Tumor Service of the Memorial Center for Cancer and Allied Diseases although not writing specific chapters as collaborators have contributed greatly by the wealth of their clinical experience in the treatment of many of the patients comprising the source material for this book.

We wish to express our grateful appreciation to Drs Leslie R. Taber James S Gallo and Abram Vermeulen of the Lendrim Tumor Clinic of the Paterson General Hospital, Paterson, New Jersey for their cooperation during that period when the authors were more actively associated with the Lendrim Tumor Clinic Some of the most interesting case reports contributing to this volume were of patients treated at the Lendrim Tumor Clinic.

The medical profession is indebted to Dr Arthur Purdy Stout for his detailed analyses of neoplasms arising within the soft somatic tissues It is largely on the basis of his original and critical studies that this group of neoplasms heretofore often catalogued into a heterogeneous group usually called spindle-cell sarcomas has been classified into histogenetic divisions on the basis of histologic criteria. We are sure that this book could not have been so specific in its recital of the natural history of these tumors and the correlation of end results with treatment were it not for the classifications so accurately established by Doctor Stout.

The microscopic diagnoses of these soft somatic tumors were made in the Memorial Hospital series by the late Dr James Ewing and by Drs Fred W

Stewart, Frank Foote, and Arthur Allen, from the Pack Medical Group by Dr George K Higgins, and from Doctors Hospital by Dr James R Lisa

We thank the following for lending us, and permitting us to publish, important illustrations Drs William W Ayers, E I Bartlett, William B Bean, J C Bielawski, James D Boyd, F A Chandler, George Erdman, Hyman I Goldstein, Jerome Gross, R E Gross, W R Hyde, Robert C Mellors, John Pool, N W Popoff, Armand J Quick, Hans G Schlumberger, S M Silverstone, Arthur Purdy Stout, M Tatelman, W L Watson, and J E White

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The artist was Mr Alfred Feinberg who has always been most helpful in applying his skillful talents to the interpretation and depiction of our surgical procedures

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Finally, Mr Paul B Hoeber of Harper & Brothers has continued, as in earlier years and with previous publications, to guide us judiciously in the preparation of this book

Go Little Book, and to the Fair impart
This Gentle Message from a Tender Heart

. . . . . .

And tell the Maid if she Vouchsafe to Look,
With curious Search in Thee, my little Book,
No Guileful Arts no Venal Praise She ll find,
But the Plain Image of an Honest Mind,
Warm Gen rous Truths which from his Bosom flow
Who ne er Forgot a Friend and can Forgive a Foe

—Richardson Pack
Exon England
May 25, 1725

SECTION I

Classification and Natural History of Tumors of Soft Somatic Tissues

Introduction

THE SOFT SOMATIC TISSUES constitute the greatest amount of tissue within the human organism. This mass of flesh situated between the epidermis and the parenchymal organs comprises over 50 per cent of the body weight The muscles alone of which there are over 400 constitute 40–45 per cent of body weight of the adult and about 25 per cent of the child s weight A large number of specific tissue types comprise the soft somatic organs These consist of connective tissue, blood and lymphatic vessels smooth and striated muscle fat, fascia synovial structures the reticulo endothelium, and others Offshoots of these tissues penetrate into every portion of the human anatomy No organ is exempt from their presence

The soft somatic tissues comprise the form and substance of the body The height the weight and the body conformation are largely determined by the distribution of these tissues The delineaments of the shape, such as the facial features are welded in a hereditary pattern by the functional equilibrium of intergrowth of these tissues

The organs composed of the soft somatic tissues are subjected to injury and disease as are any other tissues It is truly remarkable that until recently very few efforts have been made to investigate those diseases to which the soft somatic tissues are subjected. Infectious processes hyperplastic phenomena, metabolic alterations degenerative changes, and neoplastic growths may each occur within the tissues which comprise the soft somatic organs of the body

Great credit belongs to Klemperer who served to classify and offer a nosologic scheme to such apparently diversified pathologic entities of the soft somatic tissues as rheumatic fever rheumatoid arthritis polyarteritis acute lupus erythematosus scleroderma and others

Certain afflictions of muscles (muscular dystrophy) and involvement of peripheral nerves (poliomyelitis) have focused attention upon the necessity for a better understanding of diseases which afflict the soft somatic organs of the body

Neoplasms of the soft somatic tissues have, for some unknown reason, received scant attention regarding their nosology natural history and methods of treatment. This is truly remarkable inasmuch as this tissue which makes up the bulk of the human body is subjected to a host of neoplastic afflictions which vary from very benign growths to some of the most malignant. Such tumors have frequently been described by the nondescript generic heading of sarcoma and have been lumped into this nosologic repository without effort to identify further subdivide, and thereby to learn and conquer the various subdivisions

Certain of the sarcomas have been subjected to careful and critical study because of the interest of certain groups

Thus, lymphosarcoma, the malignant proliferation of the lymphoid tissue, has been carefully studied because of the interest of the internists in that disease and because of the close relationship of the lymphosarcomas to the leukemias The recent impetus in the development of chemotherapeutic agents and the initial success attendant upon the discovery of certain agents which have at least a temporary inhibitory effect upon tumors of the lymphoid tissues (the antimetabolites such as folic acid antagonists, 6-mercaptopurine, nitrogen mustard, and others) have produced a resurgence in the interest in these neoplasms

Great interest has also been manifested in the tumors arising within bone This has largely been the result of the investigations of certain schools (such as those of Bloodgood, Codman, Coley, Phemister, Jaffe, and others) into this disease process Trauma to bone and the treatment of fractures have dominated medical thought for many centuries and have probably been factors contributing to sustained investigations of the neoplastic proliferation of bone

It is indeed regrettable that no such interest has been generated in the tumors which arise within the soft somatic tissues This dearth of application has resulted in haphazard classifications, in many faulty technics of treatment, and in confusion in the literature pertaining to the natural history of the various subdivisions which comprise this group of tumors The physician today who is called upon to treat patients bearing neoplasms of the soft somatic tissues is faced with a dearth of information and a lack of proper publications which describe in detail the conduct of establishing the diagnosis, the exact therapeutic modalities to be instituted, and the expected prognosis No monographs have been published on tumors of the soft somatic tissues This is surprising in that these tumors are even more frequent than tumors of bone, for which there are a number of good-sized classic volumes At the Johns Hopkins Hospital, where Geschickter and Copeland have published two editions of their classic book, *Tumors of Bone,* malignant primary bone tumors comprise 1 0 per cent of all cancers; malignant tumors of the soft somatic tissues comprise 0 7 per cent of all cancers At the Memorial Hospital, where the Coleys have maintained a strong interest in bone tumors and from which institution Bradley L Coley recently published his volume on bone tumors, there have been 912 patients bearing primary tumors of bone, of which 592 were malignant and 320 were benign At the same institution, during a 25-year span, there have been 717 sarcomas arising within the soft somatic tissues of the body, a number in excess of the actual malignant tumors of bone

In addition to the malignant neoplasms of the soft somatic tissues, there have been thousands of patients bearing benign tumors and tumorlike proliferations arising from the soft somatic tissues

DEFINITION OF SOFT SOMATIC TISSUE TUMORS

The soft somatic tissues are those mesodermal structures which comprise the bulk of the organism and which are usually considered the organs of locomotion and support They cover the exterior of the body within the skin casement and also form the coverings of the internal viscera, such as the retroperitoneum, the mesentery, and the mediastinum The parenchymal organs are excluded, as are the bony structures Inasmuch as previous neoplastic practice has subdivided the diseases of lymph nodes into a separate category, the diseases of these organs, such as lymphosarcoma, giant follicular lymphoblas-

toma, leukemic infiltrations etc will also be omitted from this presentation. Diseases of bone marrow although this is a soft structure within the bony framework, will be excluded, as will tumors of the epithelial structures (skin) except for *certain tumors of the mesoblastic* structures of skin such as leiomyoma, dermofibroma, dermatofibrosarcoma protuberans Kaposi s sarcoma, etc. The neoplasms of nerves will be presented in this discussion for although the nerves are of ectodermal origin their anatomy and types of neoplasms most of which arise from the mesodermal component of the nervous tissues present characteristics akin to those of the other *soft somatic tissues Certain tumors* of nerve endings such as the glomus tumor fit into this category However the problem of nevi and malignant melanomas although possibly of either mesodermal or nerve-ending origin will not be presented here, as this subject requires such a vast coverage it will form the basis for a subsequent and separate publication.

An understanding of the tumors which *arise from the soft somatic structures can* be helpful in understanding tumors which arise from the cells of the supporting tissues contained within the parenchymal organs Thus, leiomyosarcomas are not infrequent within the esophagus and hemangiomas occur within the liver and kidneys Any tumor which arises from the soft somatic tissues may be present in any of the parenchymal organs as each organ will have certain supporting structures as well as neural elements and blood vessel elements within it For the most part, those tumors within the parenchyma will manifest a natural history similar to those within *the bulk of the soft somatic tissues* with certain exceptions such as the fibroma of the ovary producing a hydrothorax (Meigs s syndrome) However certain neoplasms of the soft somatic tissues which arise in certain of the parenchymal organs occur with such frequency that they have been extensively investigated and will be included in this presentation Included in this last group are the carcinosarcomas of the uterus the *adenomyosarcoma of the kidney (Wilms s* tumor) and the giant follicular myxoma (cystosarcoma phylloides) of the breast

This volume will discuss both the benign and the malignant tumors which arise from soft somatic tissues, It is necessary also to include certain tumor like proliferations which are not truly neoplastic entities but either simulate tumors clinically or sometimes develop into tumors (plantar fibromatoses) *Therefore, the clinical conduct of* patients bearing these entities would be the same as for those with certain benign tumors The diagnosis of these tumor like proliferations is mandatory for reports have been presented of needless amputation of extremities because of the mistaken diagnosis of these entities as sarcoma

NOSOLOGY OF SOFT TISSUE TUMORS

✓ The interest of James Ewing served to clarify some of the confusion which had existed concerning tumors of the soft tissues Great credit also belongs to Dr Arthur Purdy Stout for his painstaking and critical analyses of the numerous *neoplasms which comprise this group*

✓ At the combined symposium of the National Cancer Institute and the American Cancer Society held in Memphis Tennessee in 1949 the panel discussions *on tumors of the soft* somatic tissues were a milestone in efforts to understand better this oncologic entity This meeting, at which Dr Stout presided and in which some of the leading students of tumors of the soft somatic tissues participated, made an effort to subdivide vari

ous tumors of this group so that definitive methods of treatment could be developed One result of this meeting was the decision to drop the term *neurogenic sarcoma* and to substitute the neologism *neurilemmoma* (This is discussed in detail in Sect III, Chap 23) Another outstanding contribution of this meeting was the presentation of a classification of tumors of the soft somatic tissues This classification, slightly modified by us, forms the basis of the classification of tumors of the soft somatic tissues in this volume, 56 tumors or tumor-like growths are presented, of which 35 are benign and 21 are malignant Each of these growths represents an individual disease process which has its own characteristic natural history, method of dissemination, and means of growth and accordingly demands specific methods of treatment The large clinical patterns of these various processes are evident Some of the largest tumors of human oncology are included (the huge lipomas and cystosarcoma phylloides) Some of the most painful neoplasms occur here (the glomus tumor which, despite its extremely small size, is exquisitely painful and tender) Some of the growths remain locally limited, grow to huge proportions, and seldom metastasize (the dermatofibrosarcoma protuberans) Others have metastasized and are present in large numbers at the time the diagnosis is made, even though the primary tumor may be extremely small (Kaposi's hemorrhagic sarcoma) Some grow to a limited size and remain quiescent for the remainder of the life of the patient (dermofibroma), whereas others afflict the entire mesodermal and ectodermal structures of the body and produce some of the most grotesque deformities seen in human pathology (some of the disseminated expressions of von Recklinghausen's disease, diffuse neurofibromatoses) One could go on indefinitely describing every bizarre type or combination of types of affliction which are expressions of the growth patterns of this group of tumors, but each will be presented in detail under its specific heading

Despite the tremendous headway made in diagnosing these neoplasms histologically, there still remains a large number of tumors which present only characteristics of sarcoma with no criteria whatever pertaining to the tissue of origin Thus, of the 717 sarcomas which form the basis of this volume, there were 261 (36 per cent) which could not be diagnosed as to their tissue of origin by such expert pathologists as Drs James Ewing, Fred Stewart, Frank Foote, Arthur Allen, James R Lisa, and George K Higgins The situation is further compounded by the fact that the tissues of mesodermal origin maintain a high degree of versatility and may with great ease develop into any tissue of such origin

The need for a composite volume describing in detail the natural history and methods of treatment, as well as expected results, for tumors of the soft somatic tissues has stimulated us to assemble our experience in this volume During the last quarter-century, all sarcomas of the soft somatic tissues at the Memorial Cancer Center and the Pack Medical Group have been subjected to Group judgment and treatment by a group of physicians under the same professional head This experience has afforded an opportunity to survey the largest group of these sarcomas ever studied and an opportunity to evaluate the application of principles of treatment under uniform guidance These data are therefore unique because they represent not a collection of cases from various sources having in common only a uniform histologic diagnosis but are for the most part personal experiences The evolution of principles of surgical and radiation treatment over the years has been the result of collective thought and effort of a relatively few physicians under a uniform application of treatment princi-

ples The histologic diagnosis in each instance has been made by one of the following pathologists—James Ewing Fred Stewart Frank Foote Arthur Allen James R. Lisa, or George K. Higgins The large number of cases comprising each histologic group permits an opportunity to ascertain the natural history of each type The period of twenty five years embraced by this study affords adequate time for posttreatment follow ups and an estimate of prognosis for each subtype

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CHAPTER 1

Classification of Soft Somatic Tissue Tumors

THEORETICALLY the classification of neoplasms arising from the soft somatic tissues should be relatively easy All the components which comprise this group have rather individual characteristics which render them easy to distinguish The fibroblast is readily recognizable, as is the fat cell, muscle cells—both smooth and striated—have characteristics which make them identifiable, and synovial tissue, in addition to its fibrous component, contains the cuboidal cells arranged in clefts which make identification easy Despite the theoretic ease with which these neoplasms should be histologically recognizable, the converse is unfortunately true Frequently it is impossible to determine the exact histogenesis of a given sarcoma The reasons for this difficulty are many In the first instance, the more malignant sarcomas present a caricature of the parent tissue which is difficult and at times impossible to recognize The more differentiated tumors, of course, mimic in every respect the parent tissue, and in these instances the diagnosis becomes relatively easy In addition, because of the close ontogenetic relationship between the various tissues which comprise this system, each arising from primitive mesenchyme, the tissues tend to undergo metaplasia into their brother tissues under the stress of neoplasia Thus, sarcomas of striated muscle and synovial sarcomas will contain great abundance of fibrous tissue, and a close search must be made for the characteristic cell to avoid the error of listing them under the category of fibrosarcoma Furthermore, the great growth potential of fibrous tissue will cause this tissue to grow with great rapidity under the stress of the neoplastic stimulus At times the fibrous-tissue component of a given neoplasm is part of the neoplastic proliferative phase such as carcinosarcoma of the uterus In other instances there will be a great proliferation of fibrous tissue in response to the presence of the neoplasm, seen in linitis plastica of the stomach or in Hodgkin's disease This rapid and abundant growth of fibrous tissue will oftentimes camouflage the exact nature of a tumor

The diagnosis of a given tumor is rendered difficult also by the fact that the more anaplastic tissues will have differentiated along their various metabolic routes to a given point, and in those which are highly malignant the differentiation will be so scant as to be undecipherable They will then maintain the characteristics of spindle cells and fit into that repository of spindle-cell sarcoma or sarcoma of unknown histogenesis It is of interest in this respect that, in our group of 717 sarcomas of the soft

somatic tissues there were 261 which could not be identified by the most able and experienced pathologists in this form of neoplastic pathology

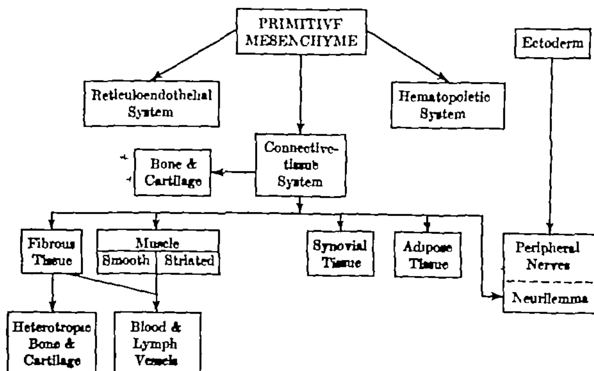
Other factors which contribute to dif ficulty in identifying certain of these neoplasms are the fact that some are organoid and as such contain numerous elements of the given organ Thus the tumors of blood vessels will contain endothelial elements smooth muscle ele

ate the different malignant variants such as in the case of malignant blood vessel tumors to recognize either the angiosar coma or Kaposi's hemorrhagic sarcoma Each of these types has its own natural history and treatment methods and offers different prognoses

Tumors may arise also from the primi tive mesenchyme in which instance a myxoma or mesenchymoma is produced.

New methods are being developed

TABLE 1 FORMATION OF SOFT SOMATIC TISSUES AND THEIR RELATIONSHIP TO OTHER DERIVATIVES OF MESENCHYME



ments, and adventitial elements such as the hemangiopericyte In their classifi cation it becomes essential to identify the cell of origin At times the tumor proliferation will produce adult type blood vessels in which case the identifi cation is easy (racemose hemangiomas) In other instances, only one element of the blood vessel will dominate the histo-logic picture and one must identify this element, such as the hemangiopericyte which will produce hemangiopericytoma, or the endothelial cell which will pro-duce the hemangioendothelioma In ad dition it becomes necessary to differenti

yearly to aid in the better identification of the various neoplasms of the soft somatic tissues Various staining tech nics such as Masson's Weigert's and others are of immeasurable assistance in aiding to identify these neoplasms The cultural studies of Stout and Murray are contributing greatly to a better un derstanding of some of the neoplasms which have avoided detection to date

Table 1 presents a diagrammatic rep-resentation of the manner in which the various tissues which comprise this sys tem are formed and their relationship to other derivatives of the primitive mesen

TABLE 2 CLASSIFICATION OF SOFT SOMATIC TISSUE TUMORS

Type of Tissue	Benign Tumors	Malignant Tumors
1 Fibrous tissue	a Fibroma b Keloid c Dupuytren's contracture Palmar and plantar fibromatosis d Peyronie's disease of penis Chronic fibrosing cavernitis e. Desmoid tumor of abdominal wall (desmoma) f Progressive fibrosing myositis (Meyenburg's disease) g Dermatofibrosarcoma protuberans	a Fibrosarcoma b Dermatofibrosarcoma protuberans
2 Undifferentiated mesenchyme	a Myxoma b Mesenchymoma	a Myxoma b Malignant mesenchymoma
3 Heterotopic bone and cartilage	Myositis ossificans	a Osteogenic sarcoma b Chondrosarcoma
4 Adipose tissue	a Lipoma (solitary and multiple) b Congenital diffuse lipomatosis	Liposarcoma
5 Blood and lymph vessels	a Hemangioma b Systemic angiomatosis c Rendu-Osler-Weber's disease d Lymphangioma e Cystic hygroma f Glomus tumor g Hemangiopericytoma	a Angiosarcoma b Lymphangiosarcoma c Angioendothelioma d Kaposi's idiopathic sarcoma e Hemangiopericytoma
6 Lymphatic and reticulo-endothelial tissue	?	a Malignant lymphocytoma b. Reticulum-cell sarcoma c Brill-Symmers disease Giant follicular lymphoma d Mycosis fungoides e Plasmocytoma f Hodgkin's disease
7 Synovial tissue	a Giant-cell tumor of tendon sheath b Synovial xanthoma c Hypertrophic arborescent synovitis of joints	Malignant synovioma (synovial sarcoma)
8 Smooth muscle	a Leiomyoma b Dermatoleiomyoma	Leiomyosarcoma

TABLE 2 CLASSIFICATION OF SOFT SOMATIC TISSUE TUMORS (*Continued*)

Type of Tissue	*Benign Tumors*	*Malignant Tumors*
9 Striated muscle	a Rhabdomyoma b Granular-cell myoblastoma	a. Rhabdomyosarcoma b Malignant organoid granular-cell myoblastoma (Alveolar sarcoma)
10 Peripheral nervous system		
a Nonneoplastic neurectodermal tumors	Traumatic and amputation neuroma	
b Peripheral nerves		
(1) Supportive tissues	(a) Neurilemmoma (b) Neurofibroma (c) Multiple neurofibromatosis (von Recklinghausen's disease)	Malignant schwannoma (Malignant neurilemmoma malignant neuroepithelioma)
(2) Secondary neoplasms		(a) Direct invasion into nerve sheath (b) Intraneural metastasis (c) Tumors of ganglia lying within nerves
c Sympathetic ganglia	Ganglioneuroma differentiated	Partly differentiated ganglioneuroma Sympathicoblastoma (Neuroblastoma)
d Paraganglionic cells	(1) Pheochromocytoma (2) Paraganglioma (a) Carotid bodies (b) Ganglion nodosum of vagus nerve	(1) Malignant pheochromocytoma (2) Malignant paraganglioma

chyme Table 2 presents a classification of neoplasms which arise from the soft somatic tissues This classification is an adaptation of the one presented by Dr Arthur Purdy Stout to the Second National Cancer Conference

An attempt has been made to develop this classification on a histogenetic basis and to include tumorlike proliferation as well as some syndromes the result of the neoplastic proliferation.

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CHAPTER 2

Incidence of Tumors of the Soft Somatic Tissues

IT is practically impossible to evaluate the exact incidence of tumors of the soft somatic tissues The difficulty is twofold Many of the harmless benign tumors such as small hemangiomas, synovial ganglia, fibromas, etc, are so innocuous as to be clinically insignificant, and many patients are either never referred for

TABLE 3 NEWLY DIAGNOSED CASES OF CANCER WITH MICROSCOPIC CONFIRMATION OF DIAGNOSES TEN URBAN AREAS OF THE UNITED STATES, 1947*

(National Cancer Institute Survey)

		Histologic Type‡		
Primary Site†	*All Types*	*Tumors of Vascular Tissue*	*Tumors of Muscle*	*Tumors of Connective Tissue*
All Sites	35,812	93	146	548
Buccal cavity	1,757	5	3	8
Digestive system	7,918	4	20	50
Respiratory system	2,469	8	3	18
Breast	4,671	2	—	7
Female genitals	5,429	1	70	11
Male genitals	1,575	1	2	4
Urinary organs	1,838	2	9	9
Skin	5,006	9	3	3
Brain and nervous system	743	18	—	101
Endocrine glands	411	—	—	1
Bone	195	5	1	131
Soft tissue	297	37	31	189
Leukemias	1,118	—	—	-
Lymphomas	1,247	-		
Other and unspecified	1,138	1	1	16

* Courtesy Biometry Section, National Institute of Health

† Classified according to the International Statistical Classification of Diseases Injuries, and Causes of Death 1948

‡ Classified according to the Manual of Tumor Nomenclature and Coding, American Cancer Society, 1951

treatment or are treated in the physician's office with no attempt at statistical enumeration.

The difficulty in ascertaining the incidence of sarcomas is the result of the failure of the various classification regimes to include sarcomas of the soft somatic tissues in their groupings Although the first attempt to obtain mortality statistics for the United States occurred in 1900 it was not until 1933 that all states recorded mortality statistics In the various codings for the report of these statistics sarcomas of the soft *somatic tissues were not listed. It was* not until 1951 when the manual of tumor nomenclature and coding issued by the American Cancer Society became available, that the various tumors of the soft somatic tissues were included as a site for indexing this type of cancer

The actuarial statistical bureau of the Metropolitan Life Insurance Company reported that in 1950 there were 559 deaths from malignant neoplasms of connective tissues of unspecified sites in the United States making the death rate 0.4 per 100 000 The total number of deaths from malignant neoplasms during the year was 210 733 with a death rate of 139 8 per 100 000

The National Cancer Institute has collected data on all cancer patients seen during 1947 in 10 urban areas in the United States Their data disclose that of 48,198 newly diagnosed patients with cancer there were 35 812 who had microscopic confirmation of the diagnosis Of this group there were 297 patients with sarcomas of the soft somatic tissues placing the incidence at 0.8 per cent of all reported cancers in that series

TABLE 4 CROSS-CLASSIFICATION OF TUMORS OF CONNECTIVE TISSUE, HISTOLOGIC TYPE BY PRIMARY SITE TEN URBAN AREAS OF THE UNITED STATES, 1947

Primary Site	*Total*	*Tumor of Fibrous Tissue*	*Tumor of Mucinous Connective Tissue*	*Tumor of Lipoid Tissue*	*Tumor of Cartilage*	*Giant cell Tumor*	*Ewing's Sarcoma*	*Tumors of Osseous Tissue NFC*	*Tumors of Serous and Synovial Surfaces*
All Sites	548	310	14	38	21	11	21	73	51
Buccal cavity	8	3	1	1	—	—	—	1	2
Digestive system	50	20	4	10	—	1	—	—	6
Respiratory system	18	6	1	1	1	—	—	2	7
Breast	7	3	1	1	2	—	—	—	—
Female genitals	11	10	—	—	—	—	—	—	1
Male genitals	4	3	—	—	—	—	—	—	1
Urinary organs	9	7	—	1	—	—	—	—	1
Skin	3	3	—	—	—	—	—	—	—
Brain and nervous system	101	98	—	—	—	—	—	—	3
Endocrine glands	1	1	—	—	—	—	—	—	—
Bone	131	13	1	—	15	9	21	69	3
Soft tissue	189	135	5	22	3	1	—	—	23
Other and unspecified sites	16	8	1	2	—	—	—	1	4

Courtesy Biometry Section National Institute of Health.

Of this group there were 37 malignant tumors of vascular tissue, 31 of muscle, and 189 of connective tissue Table 3 presents results of this survey and also indicates the number of tumors of vascular tissue, of muscle, and of connective tissue which were reported in the various other organs during this study On the Mixed Tumor Service of Memorial Center for Cancer and Allied Diseases and at the Pack Medical Group, a total of 717 patients bearing malignant tumors of the soft somatic tissues has been observed during a 25-year period Sarcomas of the soft somatic tissues comprise 0 7 per cent of all admissions to the Memorial Hospital Clinic and 0 8 per cent of all malignant tumors (Pack and LeFevre) The figure of 0 8 per cent coincides with the figure obtained by the National Cancer Institute in a survey of all malignant tumors reported from ten urban areas of the United States Table 4 presents the various tumors of connective tissue obtained for the survey by the National Cancer Institute Sarcomas in the Memorial Hospital series comprise 1 1 per cent of all malignant tumors in males and 0 6 per cent of all malignant tumors of females A significant observation is the fact that sarcomas of the soft somatic tissues comprise 6 6 per cent of all malignant tumors occurring in people under 25 years of age

The Incidence of the Various Types of Sarcomas

Table 5 presents the relative incidence of the different forms of sarcomas in the authors' series It will be observed that the greatest subdivision consists of sarcomas of undetermined histogenesis (36 4 per cent), which emphasizes the fact that many sarcomas seen to date have been in a form which precluded their exact histogenetic definition The most frequent definable sarcomas were the liposarcomas (14 6 per cent) and the rhabdomyosarcomas (13 9 per cent). Synoviomas, Kaposi's sarcomas, and malignant neurilemmomas were more or less equal in number The relatively low incidence of fibrosarcomas in this group is significant in view of the other statistics in which fibrosarcomas dominate the histologic situation Thus, in the Presbyterian Hospital (New York) series of 432 primary sarcomas of soft parts, 184 were listed as fibrosarcomas It is believed that many neoplasms catalogued as tumors of unknown histogenesis may be reported as fibrosarcomas in reports from other institutions (See Sect III, Chap 24) Angiosarcomas, comprising 2 6 per cent of the total, were the least frequently observed malignant tumors of soft somatic tissues in our series

TABLE 5 MALIGNANT TUMORS OF SOFT SOMATIC TISSUES, BY HISTOLOGIC TYPE

(Authors' Series)

Histologic Type of Tumor	*Number*	*Per Cent*
Total cases	717	100 0
Sarcoma of undetermined histogenesis	261	36 4
Liposarcoma	105	14 6
Rhabdomyosarcoma	100	13 9
Synovioma	60	8 4
Kaposi's sarcoma	48	6 7
Malignant neurilemmoma	46	6 4
Fibrosarcoma	39	5 4
Dermatofibrosarcoma protuberans	39	5 4
Angiosarcoma	19	2 6

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CHAPTER 3

The Hereditary and Congenital Occurrence of Soft Somatic Tissue Tumors

THE FREQUENT OCCURRENCE of sarcomas in young children, some being present even at birth, strongly suggests a congenital aspect of these tumors Sarcomas of the soft somatic tissues present at birth invite interesting speculation concerning their etiology and pathogenesis A cancerogen that has a maximum of nine months to effect its influence must be an extremely potent one Of the numerous theories promulgated pertaining to the nature of sarcomas present at birth, none is completely satisfactory (See Sect IV, Chap 25, Sarcomas of the Soft Somatic Tissues in Infants and Children) The fact that many of these tumors are congenital, and some are produced on the basis of the hereditary transmission of genes which influence the production of these tumors, has been definitely proved

TUMORS OF BLOOD VESSELS

Benign hemangiomas are mostly congenital tumors, and the majority are present at birth or make their recognizable appearance in early infancy In 1 of 5 patients the hemangiomas are multiple, and as many as 25 have been observed in a single patient These tumors predominate in females, usually in a ratio of 2.1 They have been observed in identical twins The appearance of the hemangiomas at birth indicates a congenital occurrence (Fig 1) Some of them may disappear shortly after birth, whereas others will grow with the growth of the organism

From the appearance of small, sometimes innocuous, localized hemangiomas, large congenital arteriovenous aneurysmal anomalies and extensive systemic hemangiomatoses occur These represent, at least in some instances, a basic defect in organization and development, and they are frequently associated with certain neuroectodermal defects Imbecility, epileptiform seizures, and neurofibromatosis occasionally accompany the systemic hemagiomas in the same patient This congenital deformity apparently represents defects in the mesodermal and ectodermal derivatives

There are several congenital neurocutaneous syndromes associated with angiomatoses which represent congenital neuroectodermal defects involving the central and peripheral nervous systems

and are chiefly found in association with hemangiomatous lesions These consist of (1) von Recklinghausen s neurofibromatosis and angiomas of the skin (2) Bourneville s syndrome with tuberous sclerosis Pringle s disease and regional angiomas and (3) Sturge-Weber s disease with cephalofacial hemangiomas (See Sect. III Chap 19 The Treatment of Tumors of Blood vessel Origin)

Hereditary hemorrhagic telangiectasia (Rendu-Osler Weber s disease) (Fig 2) is a tumor transmitted as a simple dominant affecting both sexes and transmitted through either the male or through the female, with atavistic skipping of individuals or generations

Angiosarcomas and Kaposi's hemorrhagic sarcomas although not congenital, bear a similar racial predilection in that Jewish and Italian populations are most frequently involved In the Memorial Hospital series 75 per cent of patients bearing angiosarcomas were of either Jewish or Italian extraction and 83 per cent of those bearing Kaposi's hemorrhagic sarcomas were of either Jewish or Italian extraction

TUMORS OF LYMPH VESSEL ORIGIN

Cystic hygromas are often congenital. In some of the cystic hygromas one often sees large collections or aggregates of lymphoid tissue and others with well developed germinal centers These inclusions testify to the early conjoined origin of the lymphoid tissue and the primitive lymph vascular system. It is our opinion that in patients with systemic lymphangiomatosis, these lymphangiomas which involve an entire extremity extending from shoulder to finger tips or from groin to toes probably originate with the budding of the limbs early in the development of the fetus because the neoplasm is diffusely distributed to all structures of the arm or leg

Milroy in 1892, described a family of six generations comprising 97 individuals in which 22 patients bore a type of deformity which he described as congenital lymphangiectasia The characteristics of the disorder are congenital origin steady growth corresponding to the normal growth of the body to adult size, limitation of edema to one or both extremities the area involved varying permanency of the edema entire absence of constitutional symptoms and local symptoms apart from those described Light is thrown upon the conjoined effects of both the susceptibility to a given disease and the influence of trauma upon this doomed tissue in one of his patients This man a member of the third generation was born with a large foot and had no changes elsewhere until the age of 20 when he was thrown from a carriage and sustained an injury to the sound leg Immediately after this the leg began to enlarge and continued to do so until it attained an enormous size A second patient in the third generation was normal at birth and remained so until age 12 when one ankle apparently spontaneously developed the appearance of having been sprained and presented the symptoms of pain, swelling, and tenderness without any history of trauma. All the other symptoms subsided except for the swelling, and this increased until it involved the entire foot and leg

TUMORS OF FIBROUS-TISSUE ORIGIN

The tendency of certain individuals to produce an overgrowth of fibrous tissue under the influence of various stimuli is discussed in detail in Section III Chapter 15 under Desmoplastic Diathesis. In that discussion it is shown that certain abnormalities of fibrous tissue represent localized manifestations of the generalized diathesis It is of interest in this respect that certain breeds of animals have specialized tendencies to produce tumors of fibrous tissue Thus Bos

ton terriers have a high incidence of fibrous-tissue tumors, and fox terriers have a tendency for the production of fibromas and fibrosarcomas

In the human the formation of certain tumorlike proliferations is constantly observed Thus, the keloid occurs in patients who bear the diathesis for the overgrowth of fibrous tissue It appears that this is a congenital, although not necessarily an inherited, characteristic Muscular torticollis often occurs as a congenital abnormality Hulbert has reported 100 cases of congenital torticollis and 117 with sternomastoid tumors The exact nature of these congenital defects of the sternomastoid muscle is not known, although Hulbert presents evidence that the defects may be transient and may resolve spontaneously, hence he does not advocate therapy

Dupuytren's contracture is apparently an inherited abnormality in certain instances This feature is demonstrated by the fact that 118 individuals from families afflicted with this disorder have been reported Evidence of this disease among siblings and offspring has been presented Backman and Sprogis have traced its occurrence in individuals through three generations, observing interesting evidence of chromosomal transmission Krogius has published the genealogy of a family suffering from this disorder Some authorities believe that the transmission is evidence of a dom-







FIG 1 Congenital multiple hemangiomas in premature child Peripheral and visceral lesions, some containing primitive blood islands *A* Roentgenogram showing bone destruction in multiple regions *B* Numerous hemangiomas involving the extremities and the vulva *C* Temporal tumor

inant characteristic, whereas others believe it is recessive The high incidence in males suggests that the transmission may be sex linked. A similar situation occurs in patients suffering from plantar fibromatosis A familial relationship has been reported similar to that which has been observed in palmar fibromatosis

MALIGNANT TUMORS OF FIBROUS TISSUE —FIBROSARCOMA

There are no data in the literature nor in the series reviewed here to suggest any familial relationship in the formation of fibrosarcomas The extremely low incidence of sarcomas developing

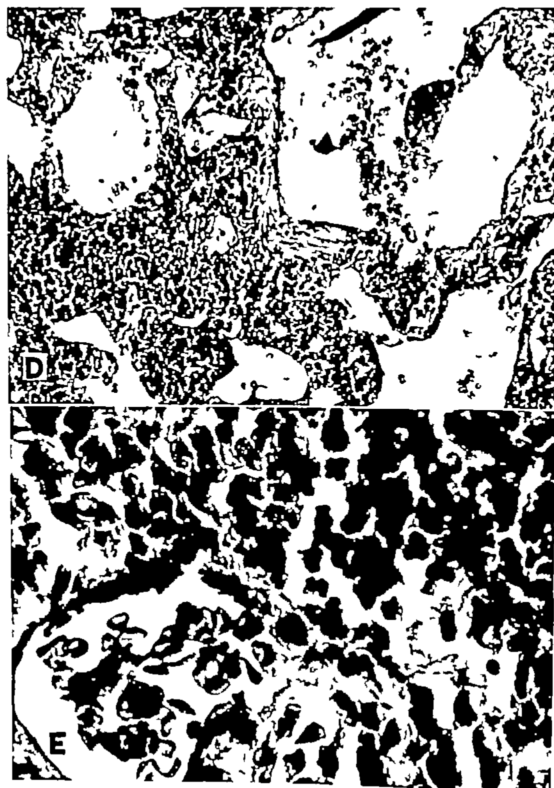


FIG. 1. (*Contd*) *D* Lesion containing primitive blood islands. *E* Higher power magnification of the congenital hemangioma in *D* showing the primitive blood islands of Pander

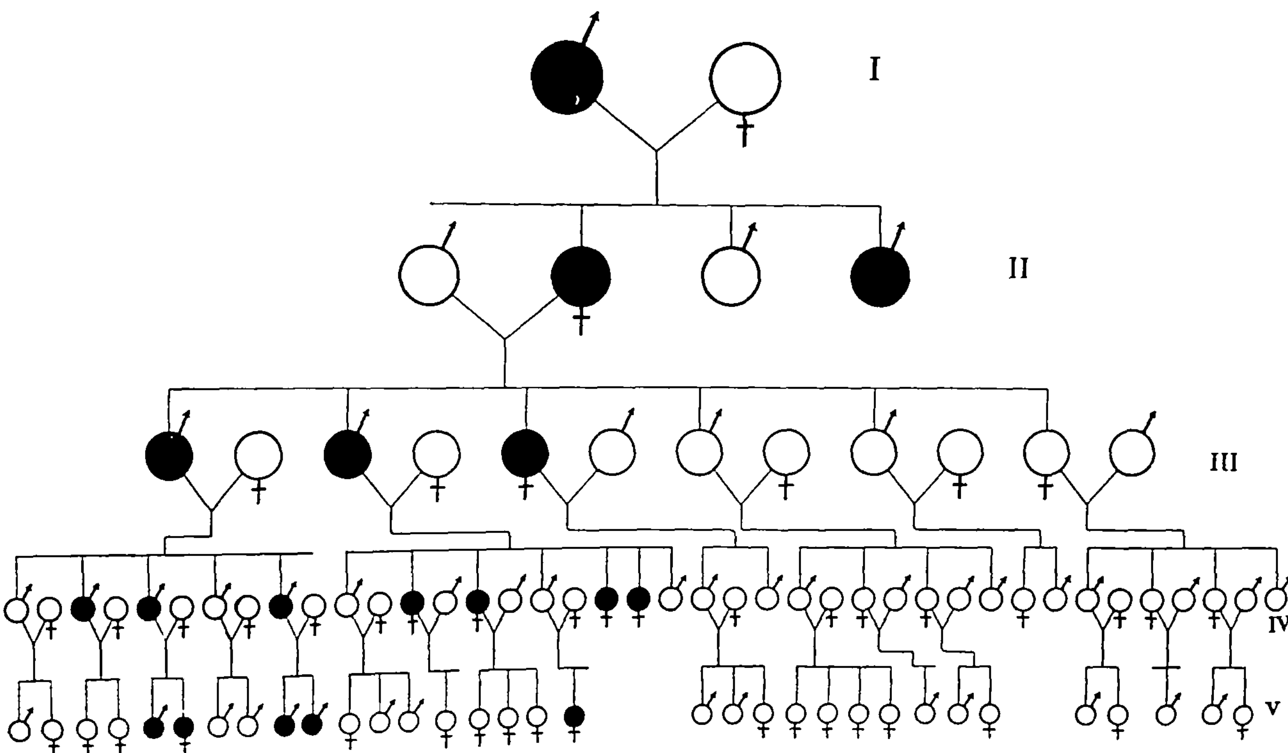


FIG 2 The genealogy of hereditary hemorrhagic telangiectasia (*Courtesy,* Dr Hyman I Goldstein)

upon any of the congenital or inherited fibrous-tissue disorders (palmar fibromatoses, etc) will indicate that the latter abnormalities cannot be considered as preneoplastic In the group of 49 patients bearing fibrosarcomas in this series, there was only one in whom a congenital relationship was suggested This was a child in whom a fibrosarcoma involving the right forearm was observed when he was 6 weeks of age He was successfully treated and remains well today, 15 years later

TUMORS OF SYNOVIAL TISSUE

There are two categories of benign xanthomatosis, namely, the infrequent, sporadic, noninherited type that occurs in adults and the classic familial type, frequently developing during childhood, usually associated with hypercholesteremia, and at times with other metabolic disturbances Gossage believed that the inheritance of xanthomatosis is from a single, dominant factor

The classic familial type presents itself in early childhood, with multiple brownish-yellow xanthomatous lesions anywhere on the surface of the body but having a predilection for the upper extremity and upper portion of the torso. Most of the lesions grow to a certain size, after which growth momentum ceases The average size is only 2 to 4 cm , but huge, grotesque xanthomatosis may occur It is believed by some that the associated hypercholesteremia predisposes to the development of the subcutaneous xanthomatosis

Malignant tumors of synovial origin are congenital in an extremely few instances In only one patient of our series, in whom a synovial sarcoma was observed when the child was only 2 weeks of age, did a congenital relationship exist There was nothing in this series to suggest any familial or inherited characteristics which predispose one to the production of malignant tumors of synovial origin

CASE REPORT NO 1 CONGENITAL MALIGNANT SYNOVI OF PREPATELLAR BU 5)

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weeks of age a swelling resembling a prepatellar bursa was noticed in the region of the left patella. It gradually enlarged. Aspiration was done but no fluid was obtained It was first excised at another institution in September 1930 It recurred in February 1931 When first seen it was a smooth movable recurrent, subcutaneous tumor 3 by 2 cm in diameter situated above the upper end of the scar overlying the patella. It was of elastic consistence, almost cystic It was attached to the anterior surface of the patella When the tumor was removed, it was bluish red in color

Operation

An incision was made over the anterior surface of the knee, the skin flaps were dissected widely back, and the tumor was dissected from its points of attachment and also to the site where it invaded the joint. Infection occurred, a pyoarthrosis and the child was treated for several weeks at the New York Orthopedic Hospital where drainage was done The pathologic diagnosis by Dr James Ewing was synovial sarcoma capable of pulmonary metastasis

There has been no evidence of recurrence The problem has been an orthopedic one. There is an 8 5 cm shortening of the affected limb and some atrophy has occurred. The function of the knee joint is very good, with complete range of motion and no limitation Some compensatory spinal curvature has occurred This end result represents a 24-year cure of a congenital synovial sarcoma

TUMORS OF ADIPOSE TISSUE

Congenital lipomatosis is a familial disorder and in many instances it has been possible to trace the hereditary pattern. Multiple subcutaneous lipomas are observed, frequently arranged in dermatome fashion. Malignant tumors of adi

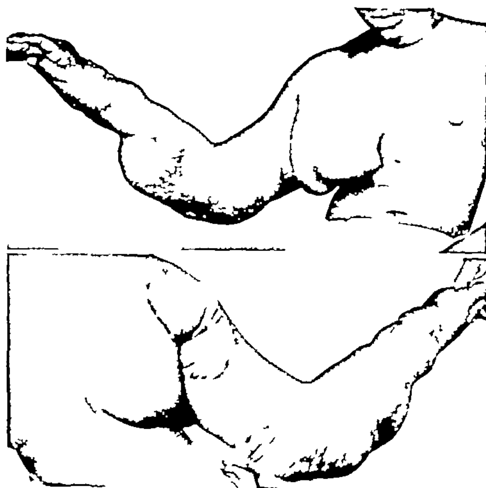


Fig. 3. Congenital lipomatosis limited to one extremity Note elongation of bones and forearm



FIG. 4 (*Upper*) Fibrosarcoma involving the right forearm of a 2-month-old infant Scar represents site of biopsy which revealed fibrosarcoma, Grade III (Patient of Dargeon, Coley, and Higinbotham) (*Lower*) Same patient 7 months after a course of x-ray therapy with complete shrinkage of tumor (Pack and Ariel, Surgery 31 443, 1952.)

pose tissue, liposarcomas, do not present any evidence that they are in any way of familial influence In this series one patient was observed with a liposarcoma that was believed to represent a congenital tumor The baby, of Puerto Rican parentage, was born with a huge tumor involving the left lower leg. The tumor was discovered at birth Roentgenograms showed extensive destruction and separation of the tibia and fibula by this interosseous tumor A formal biopsy was pronounced liposarcoma by Dr James Ewing Radiation therapy was administered through two portals, an anteromedial and anterolateral, using 140 kv, 3 mm aluminum filter, 30 cm target-skin distance, and 100 r daily alternating on successive days until a total dose of 2000 r × 2 was given The tumor completely disappeared, the bones regenerated wholly, and the patient is now well, with a functioning leg and no evidence of disease at 20 years of age This case represents the only such instance in the series of 105 liposarcomas (Fig 6)

TUMORS OF MUSCLE ORIGIN

The granular myoblastomas, chiefly occurring in the tongue, and the rhabdomyomas of the heart are definitely congenital tumors, occurring usually shortly after birth It is difficult at times to distinguish the muscle tumors of the heart



FIG 5 (*Left*) Synovial sarcoma involving the left knee in a male aged 4 months Tumor first noted at 2 weeks of age This is the youngest recorded case (*Right*) Patient 10 years after wide local excision and radiation therapy

from the glycogen storage disease (von Gierke's disease) which represents an inborn error of metabolism

Malignant tumors of muscle, rhabdomyosarcomas, are occasionally noted as congenital tumors. In one Irish American infant of this series on the day of birth a deep palpable tumor was discovered in the left quadriceps femoris muscle. It was radically excised and microscopic study revealed it to be a true rhabdomyosarcoma. He was given immediate postoperative irradiation and is now living and well fifteen years later with no



FIG. 6 (*Upper*) Clinical photograph and roentgenogram of a large interosseous liposarcoma involving the lower left leg of a child at birth. (*Lower*) Clinical photograph and roentgenogram taken 18 years after above figures showing cure of the liposarcoma.

difficult to say much about this neoplasm because of its rarity

MISCELLANEOUS TUMORS

Wilms's embryonal adenomyosarcoma of the kidney is a congenital tumor about which there are numerous theories explaining its genesis (See Sect. III Chap 15 for a discussion of the various theories pertaining to the genesis of this interesting oncologic entity) *Sarcoma botryoides* is also a congenital tumor which apparently arises on the basis of Cohnheim's theory of aberrant cells and tissue rests

HAMARTOMA

In 1904 Albrecht described a group of swellings or tumefactions resulting from congenital malformations and labeled them *hamartoma*, derived from the Greek word meaning to err or to fail. Not true neoplasms in the strict sense of the word, they are benign organoid tumefactions, comprised of a mélange of tissues peculiar to the organs in which they originate. These multiple tissues are usually of mesodermal derivation Such complex mixed-cell tumors have been found in the lungs kidneys spleen gastrointestinal tract, liver brain hand, and foot.

CHORDOMA

Chordoma is a specific tumor arising from the remnants of the primitive notochord It is a rare tumor of slow progressive growth and is characterized by a tendency to invade bone by direct extension and by its ability to recur following surgical excision. It may metastasize to regional lymph nodes and to distant viscera

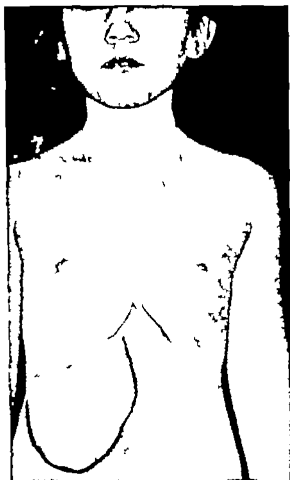



Fig 8. Hamartoma of the liver which was successfully excised. (*Left*) Clinical photograph with the size of the hamartoma outlined. (*Right*) Gross specimen of the resected hamartoma. (*Courtesy* Dr Gordon McNeer)

Virchow is credited with the initial description of this tumor in 1856 It originated in the spheroöccipital region, and because of the vacuolated appearance of the cells, he called it *ecchardosis physaliphora* In 1858 Muller advanced the theory that these tumors were derived from notochordal remnants and introduced the term *chordoma* Confirmation of Muller's view came from Ribbert in 1894 who reported five cases The first case of sacrococcygeal chordoma was described by Hennig in 1900 Thereafter, increasing numbers of sacrococcygeal chordomas were reported, and it soon became obvious that these were more common than the cranial variety The occurrence of this tumor in other parts of the spinal column has more recently been recognized by Cappell (1928) and Guthert (1939)

Harvey and Dawson's review of 240 cases of chordoma in 1941 showed the following distribution

Cranial	88 cases	36 7 per cent
Vertebral	30 cases	12 5 per cent
Sacrococcygeal	122 cases	50 8 per cent

This tumor is encountered more often in males than in females, especially in the case of sacrococcygeal chordomas Harvey and Dawson found that of the 220 cases reviewed by them 6 5 per cent were males. Gentil and Coley in a review of 128 cases of sacrococcygeal chordoma reported in the literature found that 60 per cent were males

No age is exempt Stewart and Morin found the average age of 20 patients with cranial chordomas was 35 years, whereas the age of 28 patients with sacrococcygeal chordomas was 51 years Gentil and Coley found the median age for sacrococcygeal chordoma to be 60 years

Gross Pathologic Anatomy

The tumor is generally lobular, bulky, and well circumscribed It is characterized by slow but persistent growth so that it eventually invades neighboring structures, particularly bone, and flourishes in such spaces as the nasopharynx and the retroperitoneal region The tumor is soft and vascular, and on cut section it is composed of a homogeneous and gelatinouslike tissue which in some regions shows foci of hemorrhage and cystic degeneration

Microscopic Features

The cells are usually large, polyhedral in shape, and arranged in groups or cords The large cells show vacuolation which some observers claim is due to intracellular glycogen Large islands of mucinous material may be found extracellularly, which, unlike the intracellular vacuoles, take up a mucin stain Less seldom seen features include multinucleated cells, mitotic figures, and nuclear vacuolization

Metastases by way of lymph nodes and blood stream have been reported but are unusual Widespread metastases occur in approximately 10 per cent of cases

The diagnosis of a sacrococcygeal chordoma will rarely present much difficulty It either produces a bulky mass externally or within the hollow of the sacrum When the growth tendency is posterior, the sacrum is invaded and destroyed relatively early in the disease, and x-ray studies of this region will usually show evidence of bone destruction

When the direction of growth is anterior, it will eventually result in a pelvic mass, and in the late stages a retroperitoneal intraabdominal tumor will become obvious When the tumor grows outward into the retroperitoneal space, there is room for growth, and resistance is minimal When this occurs, the diagnosis becomes more difficult, and one may be unable to differentiate it from any one of the retroperitoneal tumors

which can extend into the pelvis. It is also conceivable that a chordoma will present itself entirely as an abdominal retroperitoneal mass, having arisen either from the lumbar or lower thoracic vertebrae This occurs in approximately 5–10 per cent of all chordomas

Some examples of chordoma arising in other than the cranial or sacrococcygeal regions include the cases reported by Cappell Davison and Weil Cameron Raul and Diss and Güthert

Treatment

Chordomas are basically radio-resistant, although patients with inoperable tumors may be given prolonged palliative relief by the judicious use of radiation therapy For this purpose a protracted course of daily x ray therapy using small fractionated doses achieves the best result. Radical surgical excision of the chordoma during the preinvasive phase is the treatment of choice, and long term cures have been obtained.

SACROCOCCYGEAL TERATOID TUMOR

These complex teratoid tumors of spectacular appearance are rare neoplasms They occasionally present difficult diagnostic and therapeutic problems The sites of occurrence in the order of their frequency are the pelvis, the abdomen, the sacrococcygeal region the thorax, and infrequently the nervous system. The teratoma of the newborn usually has a disorderly arrangement of germ layers described by Ewing as a pot pourri of fetal tissues The presence of derivatives from all three germ layers in contradistinction to the dermoid tumor which is of ectodermal origin only classifies these tumors as teratomas Some teratomas may exhibit a more adult structure of their germ layers, even approaching the parasitic fetus, in whose development there is a more or less normal arrangement of organs To this group Ewing has applied the term *teratoid tumors*

A great variety of organs in various stages of development has been found e g nerves epidermis and dermoid cysts from the ectoderm bronchus intestine, pancreas liver and adrenal gland from the entoderm and fibrous tissue, cartilage, bone, and smooth and striated muscles from the mesoderm The sacrococcygeal teratoid tumors seem to be more prolific in producing rudimentary organs than those arising in other sites The bone tissue may actually condense into well formed extremities such as a forehand hand, tibia, femur or toe It requires no imagination to conceive of one of these complex sacrococcygeal tumors as the abortive half of a fused, monstrous pygopagus twinning

The teratoid tumor, with its great degree of tissue differentiation seldom undergoes cancerous transformation It has been asserted that the benignity of such a tumor can be assured if muscle twitching, peristalsis or the presence of bone can be demonstrated. This statement is practically true, but we have found several examples of embryonal cancer developing in these tumors with local recurrences after removal and distant metastases causing death

Diagnosis

In the group of published case reports these tumors are more common in females than males—a ratio of more than 3 to 1. The presence of the tumor is usually observed at birth—65 of 72 cases as reviewed by Chaffin The incidence of sacrococcygeal tumors is said to be 1 in 34,500 births The tumor may be sufficiently bulky to complicate the delivery of the infant. If the tumor is situated intrapelvically the diagnosis may not be suspected until urinary or bowel obstruction occurs

The sacrococcygeal teratoid tumor must be differentiated from a pilonidal

cyst, meningomyelocele, dermoid cyst, and congenital anal atresia A careful physical examination and roentgenologic studies usually lead to the correct diagnosis The meningomyelocele is compressible, and such pressure will cause bulbing of the anterior fontanel, furthermore, coughing and crying produce an expansile pulsation which is lacking in the teratoid tumor The discovery of extraskeletal bone in the roentgenograms establishes the diagnosis of teratoid tumor Although neurologic changes are not often associated with sacrococcygeal teratoid tumors, it should be borne in mind that defects of the spinal column, spinal cord, and membranes may occur

All sacrococcygeal teratoid tumors originate retrorectally, although they may arise dorsal or ventral to the sacrum The teratomas situated on the dorsal aspect of the sacrum (see case report following) are rare in comparison with the same tumors springing from the anterior aspect or hollow of the sacrum The origin is usually between the rectum and lower segments of the vertebral column, the tumor often grows downward to become extruded and hang as a sessile or pedunculated mass between the legs If the tumor remains within the pelvis, obstruction of the urethra and rectum may occur

Treatment

Ewing has stated that one third of the fetuses with sacrococcygeal teratoma are born dead and 90 per cent of the other infants die soon after birth Those who survive should have their tumors removed as soon as their physical condition permits The deformity itself justifies the operation Even though the tumor presents posteriorly, its growth may result in destruction, by pressure, of the gluteal muscles and fat Pressure necrosis, ulceration, and secondary infection in the tumor itself are serious complications of delay in treatment The surgeon must use great judgment in deciding the optimal time for excision The shock associated with this operation may be greater than expected The intrapelvic teratoid tumors present a more difficult surgical problem Inasmuch as these tumors are extraperitoneal and arise posterior to the rectum, the approach should never be through a suprapubic incision but rather by resecting the coccyx and, if necessary, the terminal vertebrae (Pearse). In some instances the tumor can be shelled out without sacrificing any of the lower vertebral column, but the surgeon should never hesitate to do so to assure adequate exposure and complete removal

CASE REPORT NO 2
SACROCOCCYGEAL TUMOR

A A, a male infant, 4 weeks old, was admitted to the Mixed Tumor Service at the Memorial Hospital, April 12, 1938 The delivery was reported as being normal, spontaneous, and full-term Since birth the infant had been a feeding problem, and the third successive formula was being tried A definite maternal and paternal history of twinning was obtained

History

At birth a tumor mass was observed over the lower spine and right buttock This increased in size in proportion to the child's growth The mother stated that at birth there was a small but definite rudimentary umbilical cord attached to the mass This later sloughed, leaving a small ulcer which remained unhealed The mother also noted that when the child nursed, there was a contraction over the lower portion of the mass The tumor apparently caused the infant no pain and little inconvenience

Physical Examination

The child was a well-developed, slightly undernourished male infant, with a prominent tumor mass, measuring 8 × 7 × 4 cm, overlying the lower sacrum and right but-

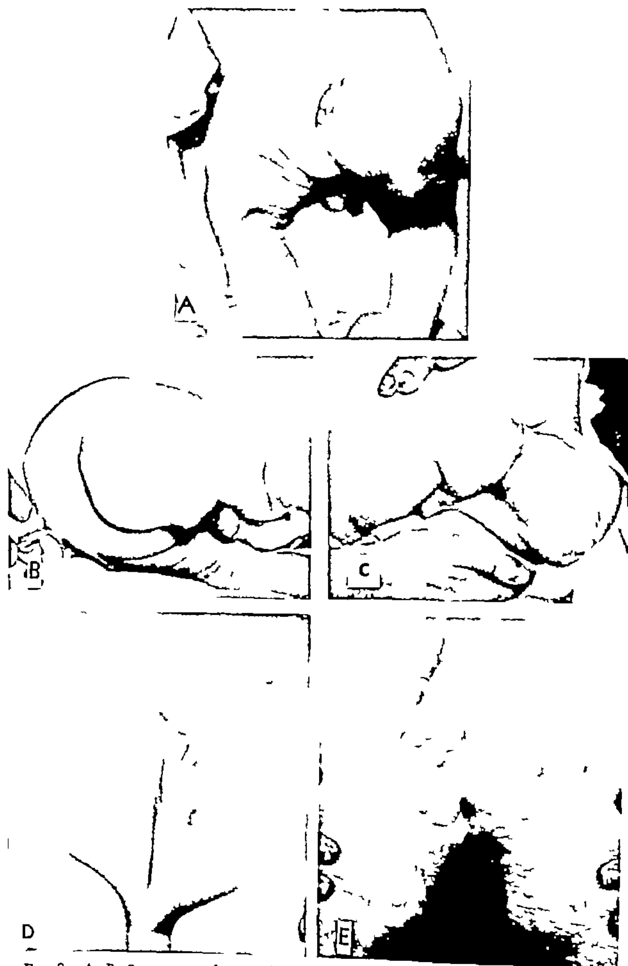


FIG. 9 A, B Sacrococcygeal teratoid tumor Infant aged 6 weeks. C Same infant, aged 13 months. Preoperative condition. D Postoperative condition. E Same patient at age 19 years. (A–D: Pack and Braund, Ann. Surg 116 761, 1942. Courtesy J B Lippincott Company)

tock The tumor was covered by intact, elastic skin except at one edge where there was a puckering of the skin which suggested a rudimentary umbilicus The presence of this navel and antecedent cord indicated a high degree of tissue differentiation approaching a parasitic fetus in character The consistency of the mass varied, in the upper portion there were several small, round fluctuant lobules, in the lower portion an irregular, firm nodule with definite skin attachment, resembling cartilage or bone Stroking of the underlying skin produced two types of motility (1) a superficial contraction of the skin, not unlike that seen in the cremasteric reflex, and (2) a deep vermicular movement similar to peristalsis within the contents of the mass The child was permitted to nurse, and on swallowing, the same contractions took place as were produced by stroking No sensory or motor changes could be demonstrated in the lower extremities There was pronounced dilatation of the superficial abdominal veins Roentgenologic studies showed no apparent defect in the sacrum and coccyx Bony shadows of different densities were visualized roentgenographically within the tumor

Treatment

Surgical removal was not considered advisable until a later date because of the age, poor state of nutrition, and general physical condition of the child Periodic examinations were made until the child was a year old, at which time he was admitted for surgical excision of the tumor During this year of observation, the increase in size of the tumor was not disproportionate to the growth of the child as a whole

Operation

Performed under ether anesthesia, April 5, 1930 The tumor was excised through a wide elliptical incision The dissection was relatively close to the capsule of the tumor, and a good plane of cleavage was encountered except at the base where there was a stalklike attachment to the sacrum Adequate skin flaps permitted closure of the wound with interrupted silk sutures A marginal stab wound was made for drainage The postoperative course was uneventful, apart from a slight wound infection near the anus The patient was discharged in good

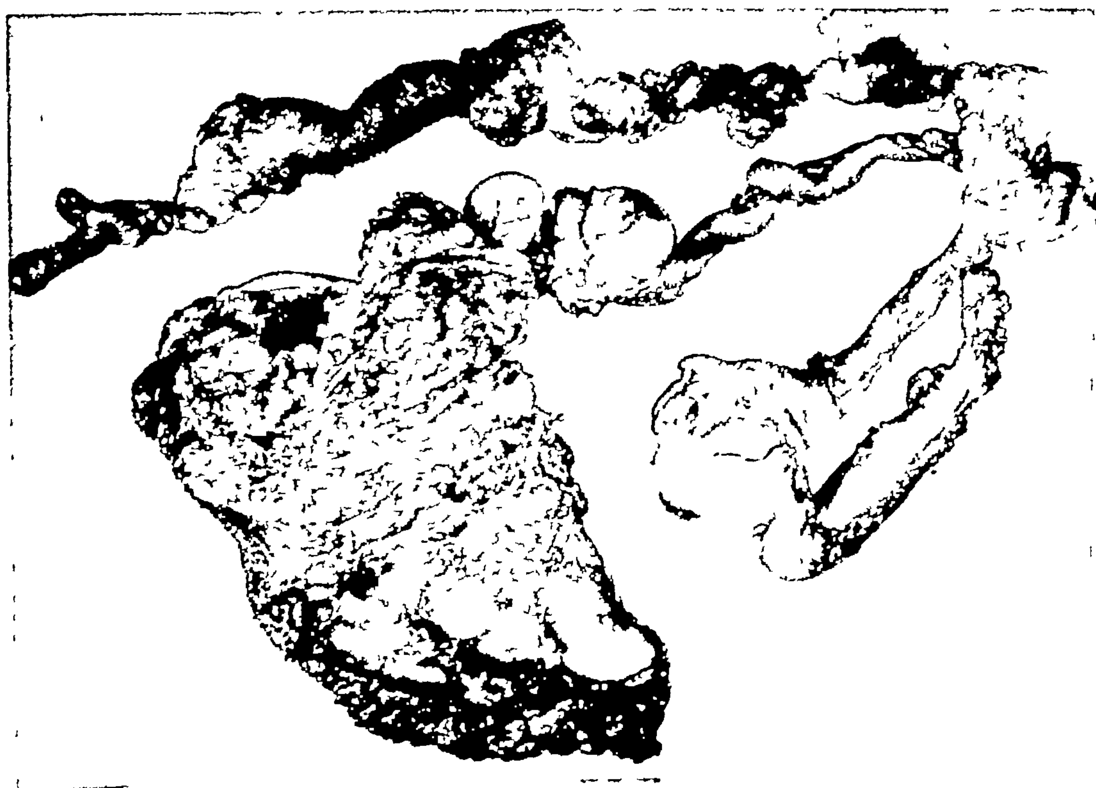


FIG. 10 Gross specimen showing 78 cm of intestine within tumor in Fig 9 (Pack and Braund, Ann Surg *116* 761, 1942 *Courtesy*, J B Lippincott Company.)

health on the seventeenth postoperative day The child was seen in October 1948 and showed no evidence of residual tumor There was only a slight central depression of the scar over the sacrum

Pathologic Examination

The specimen consisted of an excised mass surmounted by an ellipse of skin measuring 8 × 10 cm The subcutaneous tumor was made up of fat, connective tissue bone, fragments of hair and a large length of in testine which, when uncoiled, measured 78 cm in length It was divided into segments by occlusion of the lumen and contained a thick greenish mucoid substance which was chemically negative for the presence of bile Along the course of this loop of intes tine were situated three small outpocketings which contained clear thick, mucoid ma terial A fourth globular outpocket con tained clear watery fluid Microscopically this cloacal sac, or diverticulum was identi fied as a urinary bladder Microscopic study of various parts of the tumor disclosed struc tures identifiable as well formed adrenal (lacking medulla) poorly formed brain fetal fat, epidermis, well-formed urinary bladder large intestine bone cartilage and questionable bronchus

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CHAPTER 4

The Role of Trauma in Inducing Sarcomas

THERE is no group of tumors which excites more medicolegal interest than sarcomas of the soft tissues because of the reputed influence of trauma as a causal, inciting, and stimulating factor Innumerable law suits have been waged in which patients in good conscience, abetted by the testimony of well meaning but ill informed physicians have claimed compensation and disability benefits because of an asserted role of trauma in causing the tumor The sympathy of judge and jury toward a patient afflicted with a malignant tumor of questionable curability results in many verdicts favorable to the plaintiff and yet it is no exaggeration to state that in not one case in fifty is the evidence incontrovertible and the decision justifiable. The proverb "*In dubio semper pro laeso*" ("In doubt always favor the injured") achieves precedence over fact based on experience and experiment

As our fund of knowledge about neoplastic diseases increases the discovery of proved etiologic factors relegates the role of trauma more and more into the background. An example of this assertion is the now established relationship of giant-cell tumors of bone to parathyroid tumors a refutation of the commonly accepted older theory that injury provoked this tumor We must distinguish between trauma as a direct or as an indirect cause of cancer; e g we have demonstrated that sarcomas have developed in foci of myositis ossificans (see Sect. III, Chap 15) and epitheliomas have frequently occurred in the scars of major burns, indirect relationships in both instances

The prime argument against a single trauma s inciting a malignant tumor is a statistical analysis of the incidence of injuries and the rarity of reported post traumatic cancers In the United States alone there are yearly approximately ten million injuries sufficiently disabling to cause the loss of one day s work. Consider the thousands of fractured bones and the almost unheard of supervention of sarcoma. In totalizing these injuries plus the war wounds and the thousands of yearly surgical incisions the remarkable conclusion is the infrequency with which case reports are offered to support the theory of trauma.

Few case histories when subjected to critical review will fulfill the necessary five postulates governing the relationship of trauma to the origin of malignant tumors

1 The site of the injury must correspond to the region in which the sarcoma develops or it must be in the line of force of the injury as in contra coup fractures A case reported by us (Fig 12) describes the development of

a malignant synovioma of the elbow and a later osteoma of the olecranon at the exact point of injury where a baker's elbow struck a projecting iron oven door [28]

2 Proof of the injury There should be demonstrable evidence of the injury such as a bruise, a swelling, or a laceration This is a specious argument indeed, because no one has been able to prove that a massive major injury is more likely to induce the genesis of tumors than a trifling minute trauma. After all, malignant tumors usually originate in a focus of microscopic size The adequacy of any trauma cannot be asserted or denied until proof is established that a quantitative factor exists Here again the statement of the patient is usually accepted in court, but the plaintiff should always be questioned as to whether or not professional treatment was given and, if so, when in respect to the time of the accident The character of the wound may be of important significance, for example, a clean, well-healing incision would theoretically be less hazardous than a bruised, irregular, suppurating laceration or a hematoma under pressure

3 The time interval elapsing between the date of the injury and the appearance of the tumor should be compatible with a causal relationship The latent period should be neither too short nor too long For example, a sarcoma which appears either a few days or several years after an injury should not be considered to be of traumatic origin A case history is recalled of a child whose abdomen was run over by a light horse-drawn vehicle On his admission to the hospital, presistent hematuria was diagnosed as due to a ruptured kidney At operation a Wilms's embryonal adenomyosarcoma was found and removed Had the hematuria occurred six to eight weeks after the injury and had the tumor been discovered then, the etiologic postulates would have been fulfilled and judgement probably rendered in favor of the injured party

4. Ewing always stressed the importance of "the previous integrity of the wounded part" It is difficult to determine this influence one way or the other without the benefit of a record of a previous physical examination The untutored patient in his honest ignorance may not be aware of any preexistent tumor or predisposing illness The validity of a claim for compensation due to an injury reputedly causing sarcoma might be weakened if the patient with a neurilemmoma, chondrosarcoma, or liposarcoma were demonstrated to have had preexistent tumors of similar histogenesis such as neurofibromatosis, chondroma, or lipoma, respectively. Does a presarcomatous state exist, such as osteitis deformans or myositis fibrosa progressiva?

5 The character or structure of the sarcoma should be of relatively simple type, *i e*, not organoid or complex By this we mean such tumors as malignant synoviomas, liposarcomas, and fibrosarcomas in which the cell type is primitive, somatic, and structural The majority of these sarcomas do not have any causal relationship with trauma, but there have been a few authentic instances in which this possible origin seemed plausible and could not be denied nor disproved We have categorically excluded all glandular tissues and viscera, such as breast, testis, stomach, kidney, etc, and all tumors apparently originating in cell rests such as mixed or teratoid neoplasms Such simple, primitive tissues as fat, synovia, and fibrous tissue have probably reacted to injury, hemorrhage, and loss of continuity of structure by reparative hyperplasia which in rare circumstances may have become neoplastic, even malignant Certainly in individuals of desmoplastic diathesis, injuries frequently result in tumors or tumorlike states such as Peyronie's disease, Dupuytren's contracture, desmoma, keloidal fibroma, etc

Traumatic determinism calls attention to the presence of a tumor

An individual with a silent or unperceived tumor is more liable to injury at the tumor site, due to relative inflexibility of the part and unrecognized slight disability of the extremity or joint. A slight blow which would not elicit pain if directed at normal tissues will provoke pain and register disability when a pre-existing tumor is bruised or struck. It is a strange paradox that injury to a part of the body containing an unknown tumor may be an accident beneficial to the patient as it sometimes leads to the discovery of the tumor at a time when cure is still possible. Ewing applied the term *traumatic determinism* to this now well known phenomenon of predisposition of an organ or tissue to injury because of an already existent tumor and he stated furthermore that "traumas reveal more malignant tumors than they cause" A subway-car window washer who admitted no previous disability or complaints fell from a short stepladder and sustained such a severe ankle sprain that he was hospitalized. The swollen ankle and foot contained a deeper malignant synovioma verified by biopsy which was unquestionably present at the time of the accident.

Can trauma aggravate the growth of malignant tumors and hasten metastases? Many lawsuits hinging on this issue of aggravation by trauma have established that such injuries may be compensable. It is possible for a single trauma to disrupt the tumor capsule, cause hemorrhage and infection, and thereby unfavorably influence the course of these tumors, but each case should be decided on its own merits or demerits

Can trauma cause localization of metastases in the injured tissues? Theoretically the damaged tissue constitutes a locus minoris resistentiae, but the injury must occur at a time when the malignant tumor cells are embolic and in circulation—else how could they be filtered out selectively at the site of trauma and hemorrhage? We reported one instance of a young male previously treated for reticulum-cell sarcoma of the nasopharynx who injured his penis during sexual play When the resultant deep hematoma did not completely disappear but exhibited later secondary enlargement evacuation of the supposed clot showed tumor tissue, diagnosed microscopically as reticulum-cell sarcoma.

Trauma as it relates to the aggravation or the dissemination of sarcoma should be interpreted in its broad aspect. Physical trauma—either one severe injury or multiple minor injuries—is the only form of trauma usually considered in the genesis of neoplasms It is essential to consider in addition such other physical forms of trauma as irradiation (varying from actinic rays to x rays) burns and others. Chemical trauma should also be evaluated. Many forms of sarcomas have been produced by injecting different chemical carcinogens into the tissues of animals In other instances a combination of factors may be responsible for producing sarcomas Irradiated tissues in which chronic infection is induced undergo sarcomatous transformation with the formation of fibrosarcoma, rhabdomyosarcoma, osteogenic sarcoma, and others. Each agent (irradiation or infection) does not induce a neoplastic formation but a combination of agents does

Certain innocuous practices may at times contribute to cancer formation Thus the natural practice of standing, if prolonged, may result in lymphedema. This local tissue change in a susceptible individual may be a precursor to the formation of lymphosarcoma or Kaposi's sarcoma.

The influence of the various types of traumas in the formation or the enhancing of the growth of various tumors of the soft somatic tissues will be analyzed.

THE INFLUENCE OF TRAUMA ON INDUCING NEOPLASIA AND NEOPLASTICLIKE PROLIFERATIONS OF SPECIFIC TISSUES

TUMORLIKE PROLIFERATIONS OF FIBROUS TISSUE

Keloid (Cheloid)

Keloid fibroma is a fibromatous neoplasticlike proliferation of the corium and subcutaneous tissue, developing in especially susceptible dark-skinned people, usually after trauma The injury to the skin may be of major character such as a burn, it may be trifling such as a vaccination or needle puncture, or it may be apparently spontaneous, without the patient's awareness or memory of past trauma In certain African and Melanesian natives, it is a tribal custom to scarify the skin in various patterns, later enhanced by the growth of keloids conforming to the designs Negroes, members of other dark races, and Caucasian brunettes are more predisposed to this tumor than blonde persons, this is a general statement modified by exceptions, because there are definite individual predispositions

Congenital Muscular Torticollis

Various factors have been blamed as the cause of this disturbance These include neurogenic disorders, hematoma due to trauma with bleeding into the muscle, an ischemic alteration due to vascular occlusion, and physical trauma Certain authors find an increased incidence of breech presentation and of difficult and prolonged delivery associated with the presence of congenital torticollis, and they thereby ascribe a traumatic relationship to this entity Chandler states that 50 per cent of his 225 patients with torticollis were breech deliveries

Failure to find associated scarification, signs of inflammation, or other evidence of trauma in the sternocleidomastoid muscle would serve to argue against the traumatic origin of this tumefaction From the evidence at hand, it must be assumed that this congenital deformity represents a localized manifestation of some fibroblastic diathesis, with possible trauma of some nature superimposed

Dupuytren's Contracture

Dupuytren believed that the disease which bears his name was due to constant trauma to the palm and fingers Other authors have also ascribed a traumatic origin to this defect Smith, in 1884, described it in 10 per cent of 700 inmates of the London Work House Smith and Masters, in 1939, indicated a high incidence of this disease among upholsterers, serving to verify the belief of its traumatic origin Conway compiled reports from the literature and included his own material in which he correlated the degree of manual labor and the incidence of Dupuytren's contracture His study revealed that of 4,868 patients with Dupuytren's contracture, 73 4 per cent were engaged in very heavy manual labor, whereas 15 2 per cent did very light or no manual labor These data suggest that repeated traumas play a role in the development of palmar fibromatoses

Plantar Fibromatosis

As with palmar fibromatosis the exact etiology remains unknown In certain patients, who suffer this abnormality, such as soldiers, the factor of trauma is suggested, but the number of traumas unassociated with plantar fibromatosis and the fact that plantar fibromatosis

can occur without trauma would suggest that, if trauma is a factor it would be associated with some coetiologic agent. Skoog calls attention to the observations of Ledderhose who states that fibromatosis of the plantar fascia occurs after immobilization such as that incident to the treatment of a fracture These authors believe that weight bearing after a period of immobilization causes rupture of the fascial fibers which they consider a basic etiologic factor in the production of this abnormality

PEYRONIE'S DISEASE

That trauma may be of etiologic significance is suggested by the large number of patients reported by Burford, Glenn and Burford who relate a traumatic incident associated with the onset of symptoms of Peyronie's disease Of 48 patients reported by these authors 19 suffered from acute gonorrhea or chancre, 10 stated the penis was "broken" during priapism or intercourse, 4 complained of stricture, 1 had suffered surgical removal of a smaller tumor only to have a recurrence develop and 1 had an associated blood clot

BENIGN TUMORS (DERMATOFIBROSARCOMA PROTUBERANS)

Traumas have frequently been mentioned as possibly influential in the production of this growth. Irritation by a button is mentioned by Hoffmann as a presumptive cause of a tumor which developed on the volar aspect of the wrist. In our series a history of injury to the site on which the tumor arose was reported by 5 patients (13 per cent) A traumatic relationship would seem only coincidental It could have served to attract the patient's attention to a previously existing mass Again it could have served as a "trigger mechanism" in stimulating the neoplasm to appear in a person already predisposed to its development by a desmoplastic diathesis We concluded that injury as an etiologic factor played no significant role in the patients of our series

MALIGNANT TUMORS OF FIBROUS TISSUE

In a comprehensive study pertaining to the influence of wounds incurred during World War I Melzner demonstrated that a relationship between trauma and the formation of sarcoma was indeed rare, although it did occur Thies also recorded sarcomas developing in war wounds Hamant, Cornil and Mosinger recorded the development of sarcomas within operative scars One interesting report by Ivins Dockerty and Ghormley describes a sarcoma which developed at the site where the patient was kicked by a calf Meyerding from the Mayo Clinic, reported an incidence of 11.2 per cent of his patients with fibrosarcomas who had given a previous history of trauma to the site of the development of the sarcoma, although Ivins and others at a later date analyzed the material from the Mayo Clinic and did not establish this relationship In no instance in our series could a relationship be found between acute physical trauma and the formation of a fibrosarcoma

The definition of *trauma* when interpreted in its broad sense, can be considered as etiologic in the production of fibrosarcomas which occur in granulation tissues Ewing has called attention to this entity which he titled *granulation tissue sarcoma*. He stated that infection was usually present and that the grade of malignancy varied between wide limits from some that were very benign to others which were highly malignant. Stout had 36 patients with fibrosarcomas which developed either in scar tissues or at the site of a previous infection. Fibrosarcomas have been described as having occurred in burn scars chronic varicose ulcers, and even at the site of



FIG 11 Fibrosarcoma developing in a burn scar (Pack and Ariel, Surgery 31 443, 1952)

arsenic injections Figure 11 illustrates the case of a patient treated for a fibrosarcoma which developed in a burn scar.

THE ROLE OF IRRADIATION IN THE FORMATION OF FIBROSARCOMAS

There are a number of recorded instances of fibrosarcomas which developed in tissues that were heavily irradiated Stout cites four cases of fibrosarcoma developing upon radiation fibromatosis Epidermoid carcinomas developing in irradiated skin commonly exhibit spindle-cell metaplasia to such a degree that the tumors have been confused with sarcomas

THE FORMATION OF SARCOMA IN MYOSITIS OSSIFICANS

Myositis ossifications is frequently seen as a sequela to repeated trauma. The occurrence of at least six patients with myositis ossificans who developed osteoblastic and chondroblastic tumors within this tumor indicates the indirect manner in which trauma may play a role in the production of cancer That the sarcoma is quite malignant is revealed by the fact that three patients reported by Pack and Braund each had succumbed as a result of their sarcomas

TUMORS OF SYNOVIAL TISSUE

BENIGN TUMORS

The formation of synovial cysts (ganglia) is caused in some instances by trauma There is no apparent relation between trauma and the giant-cell tumors of tendon sheaths

MALIGNANT SYNOVIAL TUMORS

Of the patients with synovial sarcomas studied by the authors, nine patients gave a history of trauma preceding the development of the tumor, but in five the mass appeared very shortly after the trauma, suggesting that the trauma called attention and was not related in a causal manner One patient suffered trauma to the thigh on repeated occasions over a period of three years, after which the tumor developed at the same site and remained stationary for six years In one instance a 46-year-old

baker constantly traumatized his elbow while taking bread out of the oven. He developed a synovial sarcoma at the site of these numerous exogenous traumas

TUMORS OF STRIATED MUSCLE (RHABDOMYOSARCOMA)

Trauma plays no role in the causation of the rhabdomyosarcomas, but the limb or part containing the tumor is more predisposed to injury in fact, treatment has often been delayed due to a presumptive and incorrect diagnosis of charley horse Seven patients were able to recall some type of trauma to the approximate location in the body where a muscle tumor subsequently developed When we consider the number of bruised arms and shins which fall to the lot of the average individual, it seems safe to disregard trauma as an etiologic factor

MALIGNANT TUMORS OF BLOOD VESSELS

Kaposi's Hemorrhagic Sarcoma

Although there is no direct evidence that physical trauma per se is instrumental in the production of Kaposi's hemorrhagic sarcoma, the analysis of the occupations of the patients bearing this disease in our series revealed that most of them were employed in positions which kept them on their feet for long intervals Twenty-six patients or 73 per cent developed their initial tumors on their feet or legs, most often associated with edema of the extremities That a racial susceptibility exists is suggested by the observation that the majority of patients were of Jewish or Italian extraction That lymphedema is a factor in the genesis of angioblastic sarcomas has recently been demonstrated. Stewart and Treves have reported on lymphangiosarcomas in the edematous arms of six females with postmastectomy elephantiasis They speculated on a common systemic carcinogenic factor responsible not only for the angiosarcoma of the arm but also for the primary mammary carcinoma. Some of these lymphangiosarcomas which develop on the basis of chronic lymphedema are truly identical with Kaposi's sarcoma One such case reported by Stewart and Treves had previously been diagnosed as Kaposi's sarcoma by Dr Stewart who later



Fig. 12. A flame flash caused a sudden jerk of the arm of this baker striking the right elbow against a steel door Two tumors developed on the elbow: a malignant synovioma within 3 months an osteoma of the olecranon 1 year later Circumstantial evidence relating to possible etiologic relationship of trauma to the genesis of somatic tissue tumors. (Pack, Compens. Med. 3.5 1950)



Fig 13 Lymphangiosarcoma in lymphedematous arm following radical mastectomy



Fig 14 Appearance of Kaposi's angiosarcomatous nodules suddenly developing in donor site of skin graft

changed the diagnosis to lymphangiosarcoma

Furthermore, in the one case reported in this series and in a report of lymphangiosarcoma by Martorell from Barcelona, lymphangiosarcomas were induced in the lower extremity as a result of chronic lymphedema

The widespread dissemination of Kaposi's hemorrhagic sarcoma suggests that some systemic cancerogen may be at play or that especially susceptible blood vessels in damaged tissues may yield to the influence of this cancerogen Severe lymphedema of the lower extremities may make the tissues of the extremities more susceptible to the inception of the sarcoma In one case of our series, a sarcoma was transplanted to a donor site where a graft had previously been taken Whether this represents the actual transplantation of the tumor cells to the donor site or the formation of sarcoma upon damaged tissue cannot be definitely settled

Andervont White, and H L. Stewart have induced both benign and malignant angiomatous tumors by the injection of azo compounds and hydrocarbons into mice This indicates the feasibility of a disseminating cancerogen affecting various organisms of the body The female mice were far more susceptible than the males, which definitely establishes the influence of sex hormones in the production of certain angiomatous tumors In this respect it is noteworthy that most of the patients with Kaposi s hemorrhagic sarcoma in our series were males only three females being observed in the entire series When castration was performed on the mice, there was a marked reduction in the ability to produce tumors by the administration of carcinogens

Angiosarcoma

Little is known about the etiology of angiosarcoma except in a fragmentary way Trauma, verified by medical records was a declared factor in onset in three of our patients and in two cases reported by Stout. One therefore is logically compelled to consider the genesis of angiosarcoma from the granulation tissue capillaries of traumatized areas In two of our patients, aged 2¼ and 16 years medical records attested to the appearance of a mass in the injured area within two months Both expired within two years one of metastases from a primary angiosarcoma of the hand, and the other of metastases from a granulation tissue angiosarcoma of the temple A third patient presented a similar sequence and submitted to amputation of the arm for a sarcoma on the hand.

LIPOGENIC TUMORS (LIPOSARCOMA)

James Ewing stated, "Since traumatism to fat tissue is often followed by marked proliferation of fat cells and progressive productive inflammation it is not unreasonable to assume that under special circumstances the proliferation may take on a malignant character " Although Ewing considered trauma a reasonable explanation for the origin of some subcutaneous liposarcomas of the adult-cell type, Stout attributes to injury only a very minor role This agrees with our point of view

Considering the bruises sustained by 150 000 000 Americans yearly the likelihood of trauma s causing liposarcoma must be quite remote That it may occur is attested by case report No 3

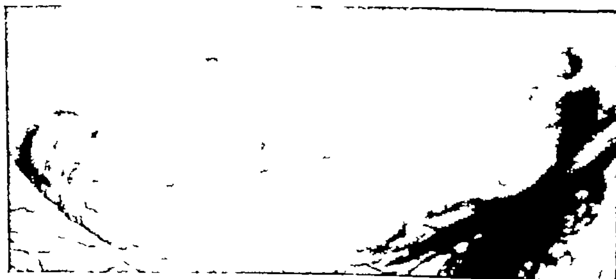


FIG. 15 Dermatofibrosarcoma protuberans. Tumor developed in scar of laparotomy incision. Treated by wide excision and postoperative irradiation. No evidence of tumor 9 years later This was the only instance of trauma which was believed to play a role in the genesis of dermatofibrosarcoma protuberans.

CARCINOSARCOMA OF UTERUS

Nothing is known concerning the etiology of carcinosarcoma of the uterus, but at least ten verified cases are on record in which x-ray therapy was administered to the uterus, usually for benign conditions twenty years before the discovery of the carcinosarcoma Whether this played a role, as it does in certain bone sarcomas, remains enigmatic

SUMMARY

Our data reveal that an occasional sarcoma is induced by physical trauma in the form of either a single severe blow or multiple minor injuries. A more definite etiologic factor is the physical trauma of irradiation Evidence is presented that a combination of factors often interplays to induce tissue changes which eventuate into sarcoma A constitutional disposition, with stasis of circulation (lymphedema), results in certain sarcomas (Kaposi's sarcoma) Trauma also plays a role in producing presarcomatous changes in certain instances, for example, myositis ossificans

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CHAPTER 5

Does a Benign Somatic Tumor Ever Become Malignant?

IT may be stated as a general rule that benign tumors of the soft somatic tissues seldom undergo malignant degeneration Conversion of a benign somatic tumor into a malignant one is denied by certain reporters who maintain that sarcomas always originate *de novo* In our experience there have been certain undeniable instances in which this transformation has been witnessed

Diffuse Fibromas

Unencapsulated and incompletely excised diffuse tumors have repeatedly recurred with increasing cellularity and anaplasia, until finally their invasive properties qualify them as malignant or fibrosarcomas Desmoid tumors of the abdominal wall diagnosed clinically and histologically as benign have recurred repeatedly (especially with subsequent pregnancies) and have even metastasized diffusely throughout the abdominal viscera Wilson has reported on a number of benign fibromas which had undergone malignant transformation

Keloids

Horton, Crawford, and Oakey report the development of a cancer in the keloid of the face of a 30-year-old female and report another such instance in the literature We have never observed one to become malignant, and none has metastasized. One patient developed a malignant neurilemmoma beneath a keloid subsequent to a scar

No Dupuytren's contractures have become malignant, but we have two cases of plantar fibromatosis which developed into fibrosarcoma Three cases have been reported in the literature of amputations being performed for fibromatosis under the mistaken diagnosis of fibrosarcoma

Fibrosarcoma

Although several authors have traced the transition of fibrosarcomas from simple fibromas, it is truly impossible to distinguish fibromas from slowly growing fibrosarcomas The low grade of malignancy and insidiousness of growth of certain of the sarcomas result in prolonged delays before the patients seek clinical attention It is accordingly difficult truly to adjudge the genuineness of the development of benign fibromas into fibrosarcomas

Two unusual instances in which fibrosarcomas developed in another form of benign lesion were observed in this

series One patient developed a fibrosarcoma within a lesion of myositis ossificans (see Sect. III Chap 15) and another unusual instance of fibrosarcoma occurred in myositis fibrosa progressiva (see Sect III Chap 15)

OSTEOGENIC SARCOMA

Shipley found four cases of osteogenic sarcoma developing in myositis ossificans traumatica Butler and Woolley noted a sarcoma developing in a calcified hematoma. Two osteogenic sarcomas were found by the authors which had developed in myositis ossificans circumscripta and a third in myositis ossificans progressiva

DESMOID TUMORS

These tumors may undergo malignant transformation into fibrosarcoma, but no instance of metastasis was encountered. They infiltrate markedly

DERMATOFIBROSARCOMA PROTUBERANS

Despite their huge size few have metastasized or become malignant—only three in our personal experience.

NEUROFIBROMATOSIS

In neurofibromatosis or von Recklinghausen s disease of the peripheral nerves at least 10 per cent of patients develop malignant nerve tumors These sarcomas are of low-grade malignancy and the cure rate is quite high. We have observed only *10* patients with multiple sarcomas of the peripheral nerves based on von Recklinghausen s disease Garre reports that *12 0* per cent of patients with neurofibromatosis develop sarcomas Couvoissier has reported an incidence of 6.5 per cent of 800 patients Charache reported 75 such instances up to 1940 Under the influence of pregnancy many neurofibromas grow larger new ones occur and a strong possibility exists that some undergo malignant transformation

ANGIOMAS

In a group of several thousand angiomas (hemangiomas and lymphangiomas) only three instances are recorded in which angiosarcomas (malignant angioendotheliomas) developed from preexisting benign angiomatous neoplasms after intervals of 18, 12, and 4 years

One patient, a 33-year-old female, had a hemangioma of the thigh treated elsewhere by x rays at the age of 15 Fifteen years later it recurred as an angiosarcoma The other two patients both aged 35, submitted to excision of a benign lymphangioma of the leg 12 years and 4 years prior to the final biopsy which was lymphangiosarcoma in both instances Both patients had received postexcisional x ray therapy over the scars

The ordinary hemangioma is benign and its transformation into a malignant tumor is so uncommonly rare that this possibility is generally ignored. Certainly it never influences the treatment of these neoplasms The hemangiomas however, by acquiring a rapidly increasing arterial supply may grow with great acceleration, become locally invasive and destructive, and kill the host by hemorrhage or sepsis and yet retain the microscopic features of benignancy We have had several instances of malignant vascular tumors developing in adult life on congenital hemangiomas and lymphangiomas The benign tumors antedated the malignant transformation Both angiosarcomas and angioendotheliomas have been identified. Preexisting benign hemangiomas of bone have changed to malignant bone endotheliomas

SYNOVIAL TUMORS

The benign giant-cell tumor of tendon sheath and the hypertrophic synovial

tumorlike arborescence which occurs around the joints have not become malignant in our experience, but we have seen instances of malignant synovioma arising from apparently benign, solid, encapsulated synovial tumors

There were three patients who had stationary masses in the hand which were completely quiescent clinically for periods of 7, 10, and 30 years, after which rapid growth occurred, and two of the three were extremely malignant These observations would suggest that some form of benign tumor of the tendon sheath underwent malignant transformation after many years of quiescence

Lipogenic Tumors

The controversial question about a lipoma ever becoming a liposarcoma may be answered in the affirmative. This complication must be judged extraordinarily infrequent if we consider the rarity of liposarcomas and the well-known frequency of lipomas The transformation occurs in lipomas which h tendency to assume bulky propo Xanthomatous, myxomatous, or c erative changes may occur in these lipomas, and in this portion of the t liposarcomas have arisen, metasta and caused death Dr James Ewing found a small spherical malignant lemmoma in the very center of a lipoma which we removed

The possibility of malignant lipc tumors' developing in preexisting b lipomas is to be admitted, but th jority of liposarcomas undoubtedly *de novo*. Liposarcomas are not see constant accompaniment of lip Stephen S Sternberg has recent ported an authentic case of liposa arising within a subcutaneous lipor

The ratio of benign lipomas to li comas is approximately 120 1 To the authenticity of a malignant c occurring in a benign lipoma, th thologist should be able to trac histologic relationship. The so-calle current lipomas may be improperly nosed True, a portion of a multilo



Fig 16 (*Left*) Angiosarcoma in thigh developing 15 years after excision and irradia of an angioma in the same region (*Right*) Excision and skin-grafting Later, metastasis bone developed

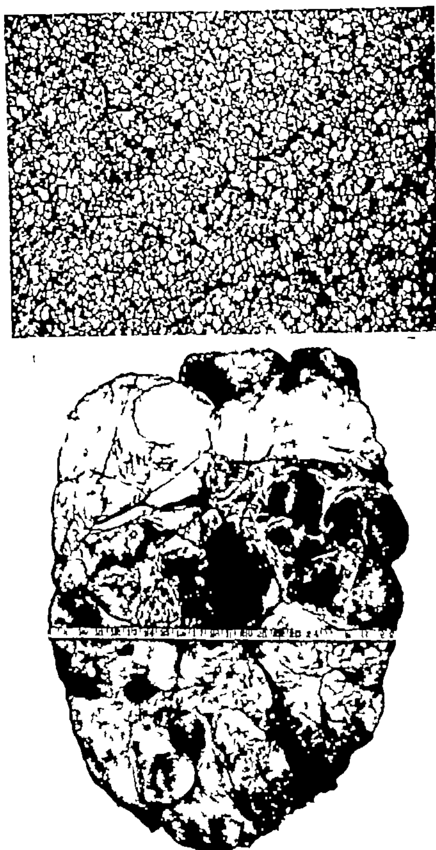


FIG. 17 (*Upper*) Photomicrograph of xantholipomatous segment of tumor shown below A liposarcoma developed in this tumor and caused death by generalized metastases. (*Lower*) Lipoma, xantholipoma, liposarcoma. Enormous tumor of thigh (see also Fig 193) Xanthomatous degeneration. Intratumoral hemorrhage Solid liposarcoma at superior pole. (Pack and Pierson, Surgery 36·687 1954)

lipoma may not have been removed originally, only to grow later, but others which recur rapidly and are found to contain foci of myxomatous tissue and cellular fat islands offer strong presumptive evidence that the lipogenic tumor was probably sarcomatous from the very beginning

In an analysis of many thousands of lipomas by the authors, there were only two patients in whom it was believed that the possibility existed that the liposarcoma had developed from a preexisting lipoma In one man a subcutaneous lipoma on the anterior aspect of the thigh grew slowly during a 19-year period and then suddenly began to grow with great rapidity When resected it proved to be a liposarcoma. In another instance a patient who had innumerable subcutaneous quiescent lipomas observed one in the precordial region to grow very rapidly It began to fungate, become infected, and bled profusely Histologic study revealed this to be a liposarcoma.

CASE REPORT NO. 3: DEVELOPMENT OF BENIGN LIPOMA INTO LIPOSARCOMA

E D, a single, white, American male, age 45 years, was first seen on April 1, 1929, complaining of a growth on the anterior aspect of the left thigh and a loss of 40 lbs in weight during the previous year

Past History

The patient consumed large quantities of alcoholic beverages He had gonorrhea in 1914 and syphilis in 1924

Present Illness

The tumor on the anterior aspect of the left thigh was first noticed ten years previously It was thought to be muscular hypertrophy In 1926 the patient was kicked on the left thigh at the level of the summit of the present tumor Local ecchymosis and soreness followed the injury, but no lump or swelling developed Four months later an elongated, painless swelling appeared and enlarged rapidly Shortly before the date of admission, there had been pain over the dome of the growth, at which point an enlargement of the veins and slight increase in local temperature were noticed His normal weight was 230 lbs

Physical Examination

The patient was obese but otherwise in good general condition There was a bulky ovoid tumor, larger than a football, extending from Poupart's ligament down to the region of the left patella When the quadriceps muscle contracted, the entire mass became rigid but moved freely over the femur. The Kahn test was four plus The blood count was normal. Radiographs of the femur showed no bone involvement The left thigh measured 83 5 cm at its greatest circumference, the right thigh measured 65 0 cm The clinical diagnosis was giant lipoma

Treatment

The entire mass was removed by sharp dissection under general anesthesia on May 3, 1929 The muscles, nerves, and important blood vessels were left intact A lateral semilunar incision was made from the external abdominal ring to the patella The tumor lay in close contact with the anterior surface of the femur throughout most of its length Enucleation was completed, and the capsule of the tumor was broken only in the region of the previous biopsy.

Pathologic Report

The specimen consisted of a large, encapsulated, lobular tumor measuring 35 × 20 × 15 cm and weighing 13 lbs The cut sections revealed a lobular structure of variable appearance The gross diagnosis was xantholipoma, possibly myxoliposarcoma Microscopically, the structure of the tumor was unusually homogeneous, considering its size The bulk of the lobules was composed of large spherical cells with scant intercellular substance The cytoplasm was

foamlike coarsely granular and contained numerous vacuoles In some regions mucinous degeneration was apparent. The histologic diagnosis was benign xantholipoma or xanthomyxolipoma (Fig 17)

Postoperative Course

The wound healed by primary intention. The relaxed tissues including the quadriceps femoris muscle regained their tone and the thigh became functionally perfect. In May 1930 the patient re-entered the hospital where a small recurrent tumor was excised from the left inguinal region It proved to be a moderately cellular radiosensitive liposarcoma. During hospitalization the patient complained of rectal pain, tenesmus, urinary incontinence and dribbling Examination of the rectum revealed a firm spherical tumor the size of an orange situated retroperitoneally in front of the sacrum and coccyx. Neurologic consultants made the diagnosis of cerebrospinal syphilis which was confirmed by laboratory tests The urinary symptoms were due to atony of the bladder associated with tabes dorsalis In November 1930 a tumor measuring 16 cm. in diameter could be palpated in the upper left abdomen it displaced the stomach upward and inward, causing a filling defect in the region of the pylorus and pars media. The patient died on March 4 1931 No neocropsy was done

Retroperitoneal Lipoblastic Tumors

In the past the majority of these tumors were believed to be benign and large series of retroperitoneal lipomas were reported. With the passage of time, many such tumors recurred not once but as often as four or five times the recurrences were deemed to be sarcomatous. It is now generally believed that the majority of benign-appearing retroperitoneal lipomas have definite foci of sarcomatous change within them and that only by careful microscopic study are these sarcomatous portions more frequently discovered. Farbman found sarcomatous changes to occur in a higher percentage of cases than in the past, e.g 47 per cent in his series covering the period 1937–1947 as compared with 14 per cent in von Wahlendorf's study in 1921. In our group of 19 cases there were only two lipomas the remainder being classified as liposarcomas.

Is the Carotid Body Tumor Ever Malignant?

The carotid body tumor is generally considered to be a benign neoplasm which consideration is based on the infrequency of metastases to lymph nodes and viscera in any reported series of cases. Instances have been recorded however of metastasis to the ovary and liver In a review of a series of 10 such tumors treated at the Memorial Cancer Center William MacComb classified 5 as benign and 5 as malignant the criteria of malignancy were infiltration of the capsule by the tumor and invasion of the lymphatic vessels

Ganglioneuroma

In 25 per cent of all ganglioneuromas, anaplasia is noted With scattered anaplasia, 18 per cent metastasize. When anaplasia occurs in one section of the tumor 65 per cent metastasize Contrariwise, neuroblastoma can maturate to a benign appearing ganglioneuroma either spontaneously or after x ray therapy

Rhabdomyosarcoma

Granular-cell myoblastomas are benign. If any become malignant, it is only by local invasion and recurrence after simple excision. No lymph node or blood vessel metastases have been recorded. Microscopically there may be cellular atypism mitosis spindle cells or a sarcomatous pattern

No transformations of rhabdomyomas to rhabdomyosarcomas have been recorded

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CHAPTER 6

Do Sarcomas of the Soft Somatic Tissues Metastasize to Regional Lymph Nodes?

ONE OF THE FIXED IDEAS which has wrongly persisted about the behavior of cancer is that sarcomas metastasize solely through the blood vascular system and carcinomas via the lymphatics The factors influencing the routes of metastasis are multiple and include the site of the malignant tumor or organ involved, the blood and lymph supply (i.e its vascularity) the invasive tendency of the tumor its growth under pressure, and the histogenesis The shape of the individual-cancer cell may partly direct the manner of dissemination, e g epidermoid carcinomas of the skin, which usually spread through lymph vessels may undergo spindle-cell metaplasia when developing in scar tissue, especially in chronic radiation dermatitis or in acrodermatitis atrophicans chronica, and in this spindle-cell form they occasionally spread widely to viscera through the blood vascular channels Although it is generally true that malignant tumors of mesenchymal derivation are bloodborne in their metastases an appreciable number of these sarcomas traverse the pathways of lymphatic drainage to lodge in regional lymph nodes In earlier years the appearance of large palpable masses in the axilla or groin of patients with a past or present history of sarcoma of the upper or lower extremity respectively was presumptively considered to be tumor thrombi in veins and therefore of fatal prognostic import, heralding the widespread generalization of the disease. Regional dissection and microscopic study of the masses have shown lymph nodes partly or wholly replaced by metastatic sarcoma The acceptance of this fact and the anticipation of this occasional occurrence now exert a definite influence in planning the scope and technic of surgical treatment It furnishes the indications and the logic for the operation which we have employed and call *excision and dissection in continuity for primary tumors and metastases to regional lymph nodes* (See Sect II, Chap 9)

THE METASTASES OF INDIVIDUAL TUMOR TYPES TO REGIONAL LYMPH NODES

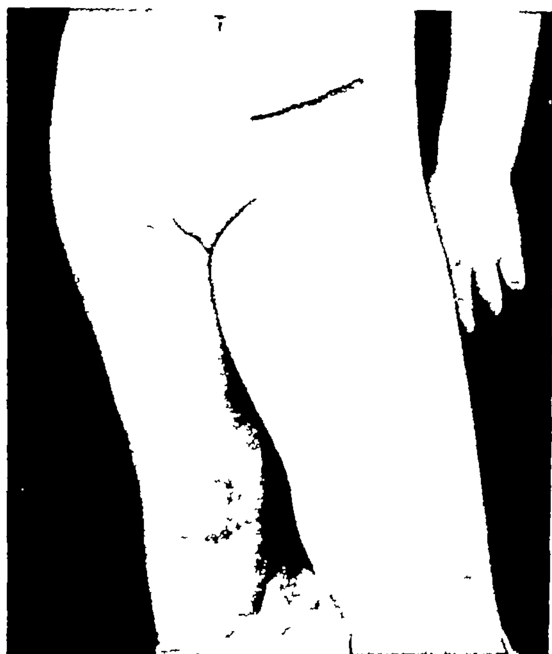


FIG 18 Metastases to the inguinal and deep iliac lymph nodes from an embryonal rhabdomyosarcoma primary in a gastrocnemius muscle in a 4-year-old girl The horizontal line indicates the upper limit of palpable tumor The enlarged inguinal nodes were noted 6 months previously, at the time the primary cancer was discovered Note moderate lymphedema due to compromise of circulation by the metastases to the inguinal and iliac lymph nodes

Synovial sarcomas have metastasized to regional lymph nodes in a relatively large number of instances Metastases were observed in the axillary and inguinal lymph nodes in 16 6 per cent of patients studied Haagensen and Stout in their review report 11 instances of metastases of synovial sarcomas to the regional lymph nodes

Angiosarcomas also metastasize to lymph nodes in a large percentage of cases In this series of patients with angiosarcoma, 45 per cent of the patients in terminal cases developed metastases to the regional lymph nodes Patients with Kaposi's hemorrhagic sarcomas did not develop any metastases to the lymph nodes in this series

It is surprising that *rhabdomyosarcomas* do not develop distant metastases more often in view of the fact that the muscle contracts so frequently, offering a means of propulsion for any tumor emboli In the 100 patients in the authors' series, metastases to the lymph nodes



FIG 19 (*Left*) Bulky fibrosarcoma which involved the lower abdomen and produced inguinal metastases (*Right*) Clinical status after surgical extirpation by wide local excision and groin dissection in continuity. (*Courtesy*, Dr Gordon McNeer, Pack and Ariel, Surgery *31* 443, 1952)

were observed in 6 0 per cent. It is noteworthy that, in those patients who were not cured of their rhabdomyosarcomas 15.4 per cent bore metastases to the lymph nodes It may be mentioned that metastases to the lymph nodes undergo the same natural history as the primary rhabdomyosarcomas and that they become necrotic and develop hemorrhagic necroses

Fibrosarcomas were observed to metastasize to lymph nodes in 3–5 per cent of all instances

Cystosarcoma phylloides although usually benign, does manifest malignant tendencies in certain instances Of the 77 patients reported by Treves and Sunderland, metastases to lymph nodes occurred in but 1 patient.

Wilms's adenomyosarcomas of the kidneys are notorious for their invasive and metastatic tendencies Of the patients of our own series 30 per cent revealed evidence of metastases to lymph nodes

In view of the fact that metastases occur to lymph nodes in a significant number of cases, this feature must be taken into account in considering any therapeutic attack upon sarcoma of the soft parts

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SECTION II

General Principles of Treatment of Tumors of the Soft Somatic Tissues

Introduction

THE SURGICAL SPECTRUM for treating tumors of the soft somatic tissues is great, varying from the simple enucleation of a benign lipoma to the most mutilating radical exeresis of major portions of the human anatomy The treatment of benign tumors (ganglion, giant-cell tumor of tendon sheath, etc.) and of tumorlike fibromatoses (Dupuytren s contracture, keloids etc.) is well defined and is presented in subsequent chapters

In any given case of sarcoma of the soft somatic tissues, the surgeon, in arriving at a choice of operation, must consider certain factors—namely the histogenesis of the tumor its degree of malignancy its fixity or mobility the original location the primary or recurrent status the presence of regional and distant metastases, and finally the experience and judgment of the operator

The first step in treatment is the establishment of a correct histologic diagnosis if this be possible. Although many sarcomas have individual clinical characteristics none is sufficiently pathognomonic to warrant a therapeutic regime without recourse to a histologic diagnosis The original surgical specimen should be obtained for selective staining and analysis if the sarcoma under treatment is recurrent. If the sarcoma is primary and previously untreated and if aspiration biopsy is not confirmative, formal incisional biopsy as the only recourse must be undertaken. An immediate microscopic diagnosis is therefore available if frozen section analysis is done, and the surgeon may proceed immediately with either surgical dissection or amputation The behavior patterns of sarcoma of different histogenetic types should be generally known by the surgeon in order that he may plan his course of action These patterns include the tendency for multicentric origin of rhabdomyosarcoma, the frequency of metastases to regional lymph nodes by malignant synovioma, the tremendous hazards of local recurrence so frequent with fascial sarcoma, the habit of angiosarcoma to metastasize early to lungs and the phenomenal radiosensitivity of embryonal liposarcoma. It is a wise precaution to secure consent for amputation prior to any operation on sarcoma of the extremities, because at the time of attempted surgical dissection, the surgeon may find that the local extent and invasiveness of the tumor preclude the possibility of cure by local excision, and amputation should not be delayed

It is essential to make a roentgenographic study of the region bearing the neoplasm. The typical roentgenographic appearance of lipogenic tumors establishes their diagnosis In other instances a tumor which on clinical evaluation seems to be superficial and to lend itself to removal by local excision will be found to infiltrate bone, making amputation mandatory Such a situation is illustrated by a fibrosarcoma of the fore-



FIG 20. Fibrosarcoma of the forearm which has invaded the ulna

arm which was found to infiltrate the ulna (Fig 20)

Radiation therapy is an aid in the management of sarcomas of the soft somatic tissues and must be given a proper place in the armamentarium of the therapist In our experience there have been instances in which technically inoperable sarcomas have received preliminary irradiation which has permitted resection and ultimate cure With a combination of radiation treatment and surgical excision, it has been possible to perform radical surgical dissections of certain sarcomas and to avoid amputation of a limb The judicious choice of surgery or irradiation or of a combination of the two for the individual patient ensures a higher percentage of definitive cures It entails some knowledge of the radiosensitivity of sarcomas of varying histogenesis and familiarity with the physical principles of irradiation in order to employ these methods of therapy judiciously

The greatest margin for error in reporting the end results of treatment for malignant tumors may be found in the classification by the reporter of a regional or histologic type of cancer as operable or inoperable The difficulty in correcting this fault is apparent when one realizes that three variable factors interplay in the pronouncement of a given neoplasm as nonresectable by any surgeon first, the condition of the patient as regards his age, the coexistence of degenerative diseases, and the complications attendant on the presence of the tumor, second, the extent of the disease (meaning the degree of local or organic involvement), the specific organ or tissue implicated, and the extension to, and incorporation of, neighboring viscera by the cancer and metastases to regional and distant sites, and third, the surgical philosophy, moral point of view, courage, and experience of the surgeon In a large group of patients with generalized bone metastases, diffuse involvement of lungs or liver, or sarcomatosis, the recognition and acceptance of inoperability is obvious to any physician But there are *numerous* other instances in which the definition of inoperability may be subjugated to careful evaluation, criticism, and even condemnation

THE POINT OF VIEW OF THE SURGEON

It is not our purpose to formulate a set of rules governing the behavior of the surgeon in a given circumstance but rather to present certain arguments for extending the scope of operability for malignant tumors The very nature of this disease, the infirm and often aged patients in whom it so frequently de-

velops and the radical character of the numerous operations designed to combat it *all conspire to make the surgical* treatment of the disease a hazardous venture for the patient and often an ordeal for the surgeon With the knowledge of the inevitability of death from malignant tumors that are not treated it seems unnecessary to state that no surgeon would refuse a patient the slightest chance for cure or even relief because *of a fear of criticism for failure* or of an unnatural pride in low figures for operative mortality

Nor should any surgeon attempt to play God and decide arbitrarily that a certain cancer patient has lived a sufficiently long life or that he has so few remaining years of even normal life expectancy that operation at best would *hardly be worth while.* We must take care in our weighty decisions concerning the denial or offering of a chance for life to a patient that in our desire not to be the executioner we do not achieve the same end results by acting as an unmoral judge For example if called upon to operate for a ruptured duodenal ulcer on a condemned criminal awaiting elec*trocution in the death row* the surgeon by his calling and in keeping with the Hippocratic oath operates with the same skill and renders just as meticulous post operative care as if his patient were to live forever

INOPERABILITY AND INCURABILITY

Many operations designed for the cure of malignant tumors achieve in too many instances only a palliative end result If inoperability were an absolute state and not a variable one, dependent in some cases on the criteria of the surgeon the term would be synonymous with incurability The unpredictable behavior of *cancers in general and sarcomas in partic*ular and the immeasurable host resistance of organs and tissues to the growth of malignant tumors combine in creating many intangible factors that make the early cancer occasionally incurable and the advanced cancer sometimes controllable. If we assume that a given sarcoma is not suitable for radiation therapy operative removal becomes the only recourse At the time of laparotomy for example a surgeon may be compelled to render judgment absolutely governing the life of the individual, the decision necessitating a matter of a few minutes as compared to days and weeks of court room deliberation by a judge and jury

The closure of an abdominal wound on a malignant neoplasm that is obviously hopeless is always done reluctantly but the abandonment of an operation that is of questionable accomplishment *must plague the conscientious* surgeon for many sleepless hours and is one of the many reasons why he remains for ever humble. He must worry whether his definition of inoperability is in his state of mind or moral courage or in the actual stage of the tumor An aggressive attack on sarcomas presenting almost insuperable technical difficulties will sometimes result in *palliative relief* and occasionally in cures, but with mounting operative fatalities Under these conditions no one would impugn the good intent of the operator

THE AGE OF THE PATIENT WITH SARCOMA

One cannot become reconciled to the perverted point of view of some surgeons who are reluctant to operate on aged patients for major forms of malignant tumors Minor sarcomas that run a chronic course may not endanger the life of the patient, but a major sarcoma should be removed regardless of the age

of the patient, providing it is technically possible and his physical state is not too precarious The anatomic and physiologic age of the subject is infinitely more important than the chronologic age At times it would seem wiser to leave the actual age off the chart or for the patient conveniently to forget the number of years he has lived if the knowledge of age alone unfavorably influences the surgeon The fitness for the surgical ordeal would then be rightly determined by the true condition of the patient as judged by physical examination and laboratory tests As examples, we have successfully performed interscapulothoracic and hip-joint amputations in aged patients for whom these operations have relieved pain and promised cures A 92-year-old physician was cured of cancer about which he was genuinely concerned

The proverbial three score years and ten, however collectively applied, do not concern us when we reach that age, because most of us, including patients, live from day to day and year to year as if we were immortal Some aged patients continue to possess a zest for life, and they merit every opportunity for cure or relief from otherwise fatal diseases regardless of advanced years, just as their rights of franchise, speech, and worship continue Rather than refuse to operate, the surgeon may justifiably modify or simplify the character of the operation

THE CONDITION OF THE PATIENT

For every argument advanced against the decision to operate on any given patient, the irrefutable defense or rebuttal is the inevitable fatality from the untreated sarcoma What would the surgeon do if confronted with an acute surgical emergency in the same patient, *e g*, a ruptured duodenal ulcer or gangrenous extremity? A patient with sarcoma, who is gravely ill from the conjoined effects of the neoplasm and intercurrent diseases, would, of course, receive medical consultation, careful deliberation concerning the choice of anesthesia, and meticulous preoperative preparation The family should jointly assume with the surgeon the responsibility for undertaking to remove a major cancer in a patient who is a serious operative risk

A critical study of over 700 personal cases of soft part sarcoma has yielded many shortcomings in the therapeutic approach to date. The fact that 39 3 per cent of all these patients bearing malignant neoplasms have been cured conclusively attests to the fact that cures can be accomplished by present-day methodology However, the observation that approximately 35 0 per cent represent recurrence and that, in Stout's series of primary sarcomas of the soft parts, there was recurrence in 61 0 per cent of his group of 432 sarcomas of the soft tissues (of which 259 were followed) pointedly demonstrates that therapy is often inadequate and that this high recurrence rate represents the result of inadequate extirpation

THE PHILOSOPHY OF TREATING DISTANT LOCALIZED SARCOMATOUS METASTASIS

Many patients with sarcomas of soft parts die of pulmonary metastases instead of complications attendant on the continued growth of the primary tumor Indeed, three, four, or five years may elapse after successful local treatment of the original tumor by dissection or amputation before the visceral metastases





FIG. 21 (*Above*) Surgical specimen of a resected rhabdomyosarcoma of the lower extremity which produced a solitary metastasis to the lung. (Pack and Eberhart, Surgery 32. 1023, 1952.) (*Below*) Laminagram of the chest revealing a solitary pulmonary metastasis from the rhabdomyosarcoma shown above. This was surgically removed by the performance of a lobectomy

become manifest It has not been an unusual experience for such patients to have no evidence of locally recurrent or residual sarcoma at the time of death Spherical metastases in the parenchyma of the lungs are undoubtedly the result of dissemination by the blood vascular system. Inasmuch as this manner of spread is probably an embolic shower of tumor cells or particles, one would naturally expect the common sequence to be the appearance of multiple bilateral pulmonary metastases Perhaps hundreds of tumor emboli may die for each one that survives and after a variable latent period grows in the new medium of the lung In practical experience, however, some patients reveal only one or two spherical opacities in a single pulmonary lobe, and these lesions, often asymptomatic, may have been discovered early through the routine check-up roentgenograms of the chest

If a sarcoma of the soft parts metastasizes to the lungs as a spherical growth and a single metastatic focus is seen, it is entirely feasible and proper to remove this tumor either by segmental resection or by lobectomy. This procedure would have been condemned a few short years ago, but we practice it today with the knowledge, born of experience, that it has definite palliative value This treatment is contraindicated in the presence of multiple growths involving both lungs or in the event that the sarcoma is infiltrative in character and causes fixation of the hilus It has frequently been claimed that the measure of palliation, *i e*, the average postoperative length of life, is generally better for the excision of secondary or metastatic sarcomas of the lung than it is for the majority of primary bronchogenic cancers

Before performing a thoracotomy for the removal of such a metastatic tumor, it is a wise precaution to employ tomography (laminagrams) by slicing the lungs radiographically in the anteroposterior and lateral sections, because by so doing additional cryptic metastatic foci come to light that were not visible in the conventional anteroposterior and lateral views of the chest The time and expense of routine laminagraphy under these circumstances may be wise expenditures if it decides the surgeons against futile attempts at palliative resection of pulmonary metastases

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CHAPTER 7

Technics of Biopsy of Soft Tissue Tumors

A BIOPSY for histologic diagnosis of all soft tissue tumors is mandatory Certain tumors which are obviously benign (lipomas etc.) and small, should be completely excised and the entire specimen submitted for histologic scrutiny

If the tumor of the soft tissues is fungating through the skin or has an ulcerated surface, the conventional biopsy may be taken by *punch forceps* or *scalpel.* In this circumstance our preference has been to use a small *endotherm loop with a bipolar coagulating current.* The current should not be strong enough to cook the small biopsy specimen. The advantages of this method are that it prevents annoying hemorrhage and possibly lessens the hazards of infection and dissemination.

If the tumor is relatively small, *complete surgical excision* may easily be done so that the entire specimen is available for microscopic study This plan is theoretically safer than the removal of a wedge or portion for analysis With knowledge based on an immediate frozen section or a delayed fixed tissue section study the surgeon may then rest content if the tumor is benign or proceed to perform a more radical dissection or even an amputation if the tumor is malignant It cannot be proved that such a delay after total excision of a small sarcoma has any appreciably bad influence on prognosis

Aspiration biopsy has been employed by us for 25 years, and we have yet to see any serious complications attending its use The technic is described as follows The skin overlying the soft part tumor is infiltrated with 1 per cent Novocain solution. The skin is barely punctured with a bistoury so that no epidermal cells will be caught within the needle A sharp 17 gauge needle is now introduced through the skin and down to the tumor, which is immobilized gently between the thumb and fingers of the left hand. A Record syringe is now attached to the needle, and strong aspiration is made at the same time the needle is advanced into the tumor This technic both aspirates and pushes a small plug of tumor tissue into the bore of the needle With suction still maintained, the needle is partly withdrawn so as to disengage the tissue plug from the tumor proper The syringe is detached, after which the needle is completely withdrawn so as not to scatter tumor cells along the pathway of the needle. The tumor plug is placed between glass slides and smeared by pressure preparatory to fixation staining, and study Considerable experience in cytodiagnosis, as well as a spirit of cooperation, is re-

quired of the pathologist With this type of biopsy, one cannot demand too specific a diagnosis, it is sufficient for the purpose if the pathologist can identify the cells as neoplastic or inflammatory and, in the case of tumor, classify it as benign or malignant Refinement of diagnosis as to histogenesis must sometimes await more detailed study after complete surgical removal of the tumor, although in many instances a definite diagnosis such as liposarcoma, synovioma, etc, can be made Hard, renitent tumors that are sclerosing and desmoplastic may not readily yield a suitable biopsy specimen In our experience a positive biopsy has always been reliable A negative biopsy by the aspiration technic is completely disregarded and naturally should not influence the subsequent management of the case In approximately 15 out of 100 sarcomas of the soft tissues, the aspiration biopsy will not secure tissue truly representative of the character of the neoplasm

Formal incision biopsies (operative biopsies) made through an intact skin have been recommended by some surgeons for deeply situated tumors This type of biopsy is done under aseptic conditions, and meticulous care is taken to suture the capsule or pseudocapsular investment of the tumor and perform layer closure without drainage of the superjacent fascia and skin We are apprehensive about this biopsy technic because of numerous cases of tragic sequelae which we have seen complicate its employment Some sarcomas are so vascular that almost intractable hemorrhage has resulted from a small biopsy incision Fungation of the sarcoma and tremendous activation of growth have followed such injudicious biopsies if an interval of time is permitted to elapse before excision is done If the condition warrants an incisional biopsy, the following compromises should be made A tourniquet is placed on the extremity above the tumor The formal biopsy is then done, and the surgeon awaits a frozen section preparation and immediate report If the tumor proves to be benign or a sarcoma of low-grade malignancy and the local conditions are favorable, a dissection may be proceeded with immediately with the tourniquet still in situ If the report indicates a sarcoma of high-grade malignancy and the local conditions are unfavorable, an amputation of the involved extremity may be done at once, always proximal to the tourniquet which is left in place This should lessen the hazard of dissemination of the sarcoma

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CHAPTER 8

Indications and Technics of Local (Limited and Wide) Excision of Tumors of the Soft Somatic Tissues

EACH SURGEON in treating a tumor of the soft somatic tissue is tempted to treat the tumor by local excision. Such a temptation must be resisted, and the operation should be planned after carefully adjudging all of the factors involved. Not only the histogenetic nature of the tumor but also its extent and degree of malignancy must be evaluated The natural history of the particular tumor as to whether it tends to be of single origin or multicentric origin (rhabdomyosarcoma) must be known. The condition of the tumor bed must be adjudged Thus a sarcoma developing in a field of previous irradiation or previous burn must be treated by complete excision not only of the tumor but also of the damaged tissue which has proved to be preneoplastic.

The high over all mortality rate from sarcomas of the soft somatic tissues indicates that if one elects to treat by local excision a sarcoma of these tissues the decision must be made only after the most critical evaluation of the situation. Instead of its being the first course of action it must instead represent a last recourse after it has been definitely determined that the more radical procedures such as amputation, are not indicated in the given situation There are no clear-cut definitions to direct the surgeon in the type of operation to perform. The decision must be made only after critical evaluation of all factors concerned and often upon the tenuous basis of clinical judgment. Certain general characteristics which serve to be followed for a given sarcoma can be briefly described.

Local surgical excision is seldom indicated for most anaplastic sarcomas especially the wholly undifferentiated rhabdomyosarcomas synovial sarcomas malignant hemangioendotheliomas, liposarcomas and the heterotopic osteogenic sarcomas These highly malignant tumors which have proved to be killers must be treated only by the boldest attack.

Wide local excision is also seldom indicated for certain neoplasms which have developed upon a damaged extrem

ity. Examples of these would be the development of lymphangiosarcomas and malignant angiosarcomas upon the edematous extremity as seen postoperatively after mastectomy In such instances the patient would better be treated by an amputation of the damaged extremity

Similarly, certain neoplasms in which the entire extremity is doomed by a congenital abnormality might better be treated by amputation rather than by wide local excision Many malignant neurilemmomas have been shown to recur proximal to the site subsequent to the extirpation of a malignant neurilemmoma of the extremity It would appear that the entire nerve element which innervates the extremity has been doomed to produce malignant tumors, and in such instances, with proof by recurrence, the better treatment would be extirpation of the entire extremity

Many neoplasms can be cured by local excision The degree of excision depends upon the same factors mentioned previously All benign tumors can be cured by wide local excision, the nature of the excision being dependent upon the type of tumor, its size, and location Thus, the simple lipoma can be enucleated, one of the few in which an enucleation is indicated Other benign tumors, such as dermatofibrosarcoma protuberans, require very wide surgical extirpation because of the tendency of the tumor to infiltrate quite extensively subcutaneously The treatment of keloids necessitates oftentimes a combination of local surgical extirpation plus x-ray therapy The treatment of hemangiomas and their various syndromes necessitates the combined utilization of local surgical extirpation, cryotherapy, injection of sclerotic agents, and irradiation The surgical treatment of certain tumors of peripheral nerves involves difficult problems of surgical technics such as the difficulty inherent in the resection of carotid body ganglioneuromas Others involve a most careful preoperative and postoperative medical regime in order to insure the success of the operative procedure, such as in the treatment of pheochromocytoma

Wide local excision of malignant tumors of the soft somatic tissues is indicated for certain sarcomas such as myxomas and dermatofibrosarcoma protuberans which grow by infiltration and very seldom metastasize, differentiated fibrosarcomas and liposarcomas, certain synoviomas, leiomyosarcomas, rhabdomyosarcomas, as well as some of the malignant tumors of peripheral nerves including the malignant schwannoma

Malignant tumors of blood and lymph vessels often develop on edematous, damaged extremities, and although they can be treated by wide local excision, amputation is often preferable In most cases of Kaposi's hemorrhagic sarcoma, surgery is not indicated, and the patient can be left comfortable and the disease controlled by irradiation.

TECHNIC OF WIDE LOCAL EXCISION FOR SARCOMAS

The decision must be made as to whether the local excision will be accompanied by a dissection in continuity with removal of the lymph nodes to which the sarcoma may metastasize It is a good policy to attempt the dissection of the regional lymph nodes in all instances in which the sarcoma is in due proximity to the nodes However, where great distances of tissue separate the two anatomic regions, the excision will exclude resection of the regional lymph nodes Analyses of the treatment policies which had been applied to certain patients bearing sarcomas, who were referred to us after a recurrence had developed, revealed that the attempted surgical excision was too limited in scope Figure 22 illustrates three of the most frequent surgical errors applied to

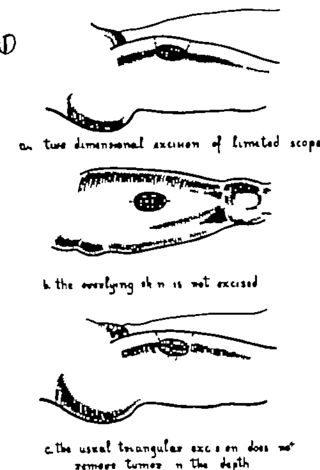


Fig. 22. Incorrect procedures commonly employed for the surgical excision of sarcomas. The excision in each instance is entirely too limited.

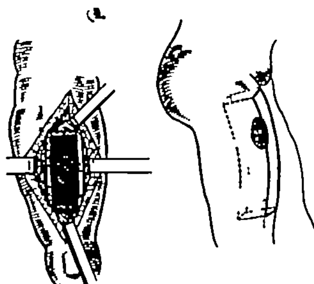


Fig. 23. The correct method of wide local excision which is three-dimensional in scope indicated for such tumors as differentiated fibrosarcomas and myxomas. Note the length and depth of the excision.

treating sarcoma of the extremities These include (1) utilization of the often practiced triangular incision which does not remove tumor in the depth and is entirely too limited, (2) not resecting the skin superjacent to the sarcoma, and (3) planning the surgical attack on a two-dimensional plane. Figure 23 illustrates a three-dimensional excision utilized for the more differentiated sarcomas

Many sarcomas are soft, cellular anaplastic, and vascular and sustain the reputation at least of metastasizing readily with slight trauma. If such a tumor is to be attacked directly by local removal, the dissection should be performed with meticulous gentle care, and retraction should always be *away from* rather than toward the tumor The soft tissues encompassing the lesion should never be compressed or handled roughly If the sarcoma is located on an extremity a tourniquet is applied proximally well above the sarcoma. It remains in place while the biopsy is being done and during the subsequent local removal. If the attempt at local removal fails either because of technical difficulties or because the surgeon realizes the futility of the effort, an immediate amputation is performed *below* the level at which the tourniquet remains applied.

Gross and microscopic study of the veins removed with the specimen not infrequently reveals the presence of intravascular tumor thrombi, which theoretically might easily have been dislodged during the trauma of the operation or could have propagated centripetally into larger venous channels On several occasions we have removed masses in the femoral trigone under the clinical diagnosis of metastatic sarcoma in lymph nodes only to find that the sarcomas were tumor thrombi growing in the larger venous tributaries These observations have influenced our colleague, Dr Robert J Booher in formulating a principle for the routine ligation of the axillary or the superficial or deep femoral veins prior to the local dissection and removal of sarcomas of the extremities If such ligations are valuable



FIG 24 A A wide exposure for a local excision of a myxoliposarcoma of the palm of the hand Only by such exposure can decision be made as to whether local excision or amputation is the procedure of choice *B* Indicates incision utilized to obtain the necessary exposure

prophylactically in the case of ordinary phlebothrombosis, they should be even more so if they delay or stop the systemic dissemination of sarcomas of the extremities

If the region of the tumor has been explored but the lesion not removed, if a formal incisional biopsy has been done, if a previous excision has been followed by recurrent growth of the residual tumor, or if fungation of the sarcoma has developed through the wound and the surgeon nevertheless decides that he will attempt a radical dissection, the one imperative technical necessity is that a wide encompassing elliptical excision of skin be made far beyond the limits of the original scar Not only the scar in the skin but the scarred tract of the incision down to the tumor must be removed in continuity with the sarcoma because of the very real danger of implanted tumor cells within the previous incision Some sarcomas grow under tension within their capsule or pseudocapsule, and a break in this barrier may encourage unrestrained growth of the neoplasm along the cleavage plane of the incision

Although not always possible of achievement, a good rule to follow is to remove the sarcoma without seeing or encountering it, by this we mean that the investiture of the neoplasm by muscles, fat, and fascia remains inviolate and that the line of dissection is grossly well beyond the palpable limits of the tumor in all directions Many sarcomas are spherical, oval, encapsulated, or pseudoencapsulated, and the temptation simply to enucleate them is great; the ease with which such tumors can be shelled out and their apparently complete localization give the surgeon a false sense of security In the compromise of selecting local removal over amputation for these malignant tumors, the surgeon should not relax his vigilance in accepting simple enucleation as an easy substitute for the always essential radical dissection In more recent years we have routinely removed the entire group of muscles involved by or encompassing the sarcoma from their origins to their insertions This precaution is especially warranted in the case of the rhabdomyosarcomas and intermuscular liposarcomas If the sarcoma is on an extremity, the order of the dissection is from above downward, *i e*, disengaging the superior limits of the tissue dissection first If the sarcoma is situated near the attachments of muscle or fascia to bone, we invariably remove the periosteum at this site and in some instances chisel away the cortex of bone We believe this lessens the hazard of local recurrence

In these radical local removals, ruthless removal of adherent or implicated arteries and nerves is practiced In the

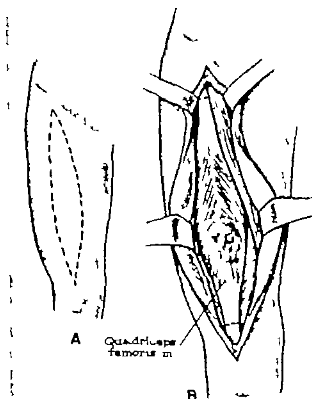


Fig 25 Exposure for the excision from origin to insertion of entire muscle which harbors such tumors as rhabdomyosarcoma or liposarcoma. If a group of muscles is involved, the entire group is similarly excised *in toto*

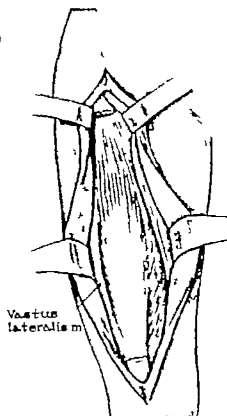


Fig 26 The appearance after the excision of the quadriceps femoris containing the tumor

case of sarcoma of an extremity partial loss of function is not too great a price to pay in lieu of amputation for the preservation of the limb in the treatment of an otherwise lethal disease For a consideration of the indications and limitations of arterial ligations, the section on this subject should be consulted. For a consideration of the principles and technic of nerve anatomoses, the section on tumors of the peripheral nerves should be reviewed.

Sarcomas of the chest wall should be attacked most aggressively at the initial attempt in an all-out effort to cure, inasmuch as one cannot resort to amputation if recurrence develops Because of adherence to ribs or intercostal extension of the sarcoma, radical removal of large segments of the thoracic bony cage is occasionally necessary but the resultant wound can be closed by thoracoplastic measures Rib resections sliding skin flaps, transposed muscle groups and free fascial transplants can close the surgical defects

The same technical difficulties are encountered in the surgical treatment of sarcomas of the abdominal wall. The surgical excision of some sarcomas of the abdominal parietes is a formidable



Fig. 27 (*Left*) A bulky rhabdomyosarcoma which has been treated by complete extirpation of the entire muscle as shown in Fig. 25 (*Right*) Postoperative appearance showing extent of incision. (Pack and Eberhart, Surgery 32.1023, 1952.)



FIG 28 (*Left*) Preoperative appearance of systemic angiomatosis involving the right lower extremity (*Center*) Photograph taken at the time of operation, indicating the extent of resection (*Right*) Postoperative appearance

undertaking, requiring the sacrifice of large muscle groups and fascial planes, in many patients the entire thickness of the abdominal wall must be excised, and the problems of wound closure are troublesome In another section we have reviewed our experience with approximately 400 tumors of the abdominal wall

The retroperitoneal tumors are usually neurogenic or lipogenic (schwannoma, ganglioneuroma, lipoma, liposarcoma) and may assume bulky proportions before evoking symptoms leading to their discovery The technical difficulties in their removal are usually surmountable, although at times a repair or even excision of the inferior vena cava is necessary The proclivity of these retroperitoneal tumors to recur locally is well known The common retroperitoneal and mediastinal lymphomas will not be discussed in this connection because of our initial policy of deleting the subject of tumors of the lymphoid series from this monograph The intrathoracic schwannomas, ganglioneuromas, and lipomas are generally located in the posterior mediastinum, their surgical removal is a comparatively easy feat Excluding lymphomas, the most frequently encountered tumor in the anterior mediastinum is the dermoid inclusion cyst

VASCULAR LIGATIONS IN REMOVAL OF SARCOMAS OF THE SOFT SOMATIC TISSUES

The fragile, nonresistant veins are so often compromised by sarcomas which are attached to or invade them that their excision is generally performed as a matter of expediency and safety The venous system is so rich that the sacrifice of peripheral veins generally causes no circulatory disabilities In surgical dissection of huge sarcomas of the groin, iliac fossa, and axilla, the femoral, iliac, and axillary veins, respectively, are commonly removed en masse with the tumor, from which they are often inseparable Slight edema of the extremity is a small compensatory penalty for the greater safety this radical measure affords The

postoperative edema is usually less after excision of these important veins than if the veins are partially or intermittently obstructed Both internal jugular veins have been removed at one time during bilateral neck dissections performed in one operative séance without unpleasant postoperative sequelae, the vertebral veins apparently compensate so well that not even a significant rise in spinal fluid pressure follows this operation. Retroperitoneal tumors chiefly the ganglioneuromas and liposarcomas may so adhere to or envelop the inferior vena cava that its segmental excision is necessary in order to remove the lesions in their entirety If the segment of inferior vena cava is removed distal to the level of entry of the renal veins no serious aftermath should ensue provided a long stump of inactive vein is not left in which stasis and thrombosis can develop Retroperitoneal and pancreatic sarcomas may so intimately involve the indispensable superior mesenteric vein that a diagnosis of inoperability has usually followed, but with continued improvement in the technic of portocaval shunts and vein grafts, this contraindication to complete removal of such tumors will soon not exist.

The sudden and complete ligation of large and important arteries entails the risk of gangrene but if the companion vein is tied or excised simultaneously and the surgeon employs sympathetic nerve block immediately and repeatedly in an attempt to overcome the usual vasoconstriction the terminal tissues may have an infinitely better chance of survival When such vascular disorders as arteriosclerosis etc., are present in elderly patients, the removal of arterial segments with the sarcomas may lead to unpredictable and disastrous consequences

Fortunately the arterial wall is less permeable to tumor invasion than the less important veins and segmental excision of arteries is less frequently necessary than for veins The adventitial wall of the artery is easily peeled away from the tunica muscularis, and the artery proper can often be preserved during local excisions for tumor of this character If the arterial wall is truly implicated by the sarcoma, then one of two decisions must be arrived at, namely either to amputate the extremity (if this be the case) at the level of election or to excise the necessary segment of artery if it can be done safely The other reasons for deciding on local excision rather than amputation for a particular sarcoma in this situation are considered elsewhere

The surgeon who deals with these problems must have sufficient familiarity with the surgical anatomy of the peripheral circulation to act decisively and safely when confronted with these especial situations

Sarcomas in the neck and carotid body tumors may require excision and ligation of the common carotid, internal carotid and external carotid arteries or of all three vessels at the bifurcation The complications of these procedures are dealt with more fully in the chapter on carotid body tumors Division or segmental excision of the common carotid artery is less dangerous than combined ligation of the external and internal carotid arteries because with the carotid bulb intact, retrograde circulation through the branches of the external carotid artery can furnish the internal carotid artery with a flow of blood sufficient to nourish the corresponding hemisphere and prevent hemiplegia or death This collateral circulation supplemented by the communication of the vertebral artery with the circle of Willis seldom is enough to prevent cerebral complications especially in elderly patients The liberal use of Novocain infiltration around the carotid bulb and sinus may prevent troublesome reflex disturbances

Operations short of amputation for sarcomas in the infraclavicular pectoral, and axillary regions may require seg

mental excision and ligation of the subclavian or axillary arteries The collateral circulation for the subclavian artery is through the thyrocervical trunk and internal mammary arteries, therefore the superior limit of the ligation should be distal to these branches In ligating or excising the axillary artery, the operation should be proximal to the origins of the subscapular and two circumflex humeral arteries, because ligation distal to these branches has resulted in gangrene of the hand Ligation or excision of the brachial artery may be fraught with hazards unless the surgeon is well aware of the anatomy of this vascular tree If the brachial artery is severed distal to or below the profunda brachii and the superior ulnar collaterals, the degree of ischemia may be tolerable, but gangrene of the hand can ensue if the ligation is below the circumflex and above the superior profunda branches

In the excision of sarcomas of the groin, one may sacrifice either the superficial or deep femoral arteries if necessary, but the loss of the common femoral artery entails considerable risk Collateral circulation after ablation of the common iliac artery is routed through the middle sacral arteries, the lumbar arteries, the superior hemorrhoidal artery, the superior and inferior epigastric arteries, and the internal mammary artery If the tumor deep in the iliac fossa has not already partly or completely compressed the vessel for a time sufficient to allow collateral circulation to develop, the sudden excision of the common iliac artery may terminate in gangrene Excision of the external iliac artery may be within the realm of safety, because the hypogastric artery can feed the femoral by way of retrograde flow through the circumflex iliac profunda and the deep epigastric arteries If the femoral artery is removed with the adjacent tumor, dependence is placed on collateral branches communicating with the popliteal arteries through the medial circumflex and inferior gluteal arteries. When the tumor is located lower in the femoral trigone and its removal necessitates excision of the femoral artery and vein, the preservation of the deep femoral artery allows an additional perforating branch to communicate with the popliteal artery

Sarcomas of the popliteal space are difficult to remove surgically because of close proximity to joint capsules, nerves, and blood vessels Injury to, ligation, or excision of the popliteal artery involves great risk because the collateral circulation at this level is extremely poor The segment of artery excised, when necessary, should be limited to that portion between the superior genu medialis and lateralis and the inferior genu medialis and lateralis Tumors involving the leg below the knee may require the sacrifice of one or more of the three important arterial branches if the lesion is to be removed by dissection The anterior tibial artery can be ligated with impunity and so can the posterior tibial branch provided the opposite tibial and the peroneal arteries are preserved If, however, the posterior tibial and peroneal arteries are excised, the ischemia of the limb becomes very pronounced and dangerous

With the great improvements in vascular surgery, it is now possible to dissect and remove many tumors previously considered inoperable because of inseparable adherence to such important arteries as the common carotid, popliteal, common femoral, superior mesenteric, and even the abdominal aorta Autogenous venous grafts to bridge defects in arteries differ from homologous arterial grafts from blood vessel banks or human donors in that the venous transplant is not relined by new endothelium nor is the wall replaced by fibrous tissue The innovations in this field of surgery promise revolutionary changes in the surgical treatment of hitherto inoperable tumors

Arterial ligation to stop dangerous or even exsanguinating hemorrhages from inoperable sarcomas is another useful indication It serves a palliative purpose even when the neoplasm cannot be removed. This principle is not new Its modern employment is found more monly in ligations of the external c artery for sarcomas of the face anc tions of the internal iliac arteri bleeding sarcomas of the uterus vagina

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CHAPTER 9

The Principle of Excision and Dissection in Continuity for Primary and Metastatic Sarcoma

IF a sarcoma of the soft somatic tissues metastasizes by way of the blood stream to the viscera, then all hope of cure by any method must be abandoned But if the sarcoma metastasizes via the lymphatics to regional lymph nodes, as some of them occasionally do, *i e*, synovioma, liposarcoma, rhabdomyosarcoma, and angioendothelioma, it is still possible to plan a surgical procedure which will remove both the primary sarcoma and the secondary manifestations of the disease in the regional lymph nodes and to give the patient an opportunity for survival In the past several years we have consistently planned each operation for sarcoma of the soft parts so as to include en masse both the primary and metastatic tumors by the procedure which we refer to as excision and dissection in continuity The first well-planned operation for cancer was conceived independently by William Halsted and Willy Meyer for carcinoma of the breast No surgical principle to date has been more important than the one conceived for radical mastectomy, because this operation allows for the removal of primary cancer, the secondary deposits of the cancer in the regional lymph nodes (namely, the axilla), and the intervening lymphatics en masse This same principle should equally apply in the treatment of all malignant tumors which mestatasize through the lymphatics to regional nodes, *e g*, carcinomas, melanomas, and less frequently, sarcomas of the soft somatic tissues

The same surgeon who will invariably perform a radical mastectomy or an abdominoperineal rectal resection for cancers in these locations apparently is content to perform the most limited type of excision or enucleation for sarcomas of the soft parts These tumors tend to recur locally with such high frequency and to metastasize to regional nodes occasionally that it is imperative for every surgeon treating them to realize the extreme importance of applying radical surgical principles The operation, therefore, should be planned to be as radical as that for other types of cancer This requires considerable ingenuity, because the somatic sarcomas are so variable in their location and are capable of draining into so many different groups of regional lymph nodes The treatment of these tumors necessitates careful study of the anatomy of the lymphatics in all parts of the body

If the sarcoma is situated closely adjacent to the group of lymph nodes into which it may metastasize, then the scope of the operation may be so planned as to enable the surgeon to remove the primary tumor and the regional lymph nodes in one encompassing excision of skin and deeper structures. The procedure entails a wide sacrifice of skin overlying the sarcoma and an extension of this skin excision to include the skin overlying the lymph nodes. The skin flaps are then dissected widely back, and in the process the subcutaneous tissues are stripped from the skin. The underlying fascia is then removed together with the specimen and the enveloping muscles, and the dissection is carried to the lymph-node-bearing regions where a meticulous and radical dissection is performed. Various bizarre-shaped incisions will result, depending on the exact location of the sarcoma. As a rule the wide dissection of the skin and removal of so much subcutaneous fat and fascia will enable the surgeon to approximate the skin margins without employing a skin graft. The excised surgical specimen includes in continuity the primary sarcoma, the skin overlying it, the subcutaneous tissues and fascia containing the lymphatics intervening between the sarcoma and the regional nodes, the muscles and deep tissues enveloping the tumor and all of the fat, lymphoid, and areolar tissues in the region of the first relay of metastases.

This procedure, of course, is not feasible when a long distance intervenes between the primary tumor and the regional lymph nodes. For example, in the case of a sarcoma of the hand or foot with metastasis to the axillary or inguinal lymph nodes, the average surgeon may be loathe to apply a principle so radical as the removal of the entire limb. Nevertheless, a disarticulation of this limb together with a groin or axillary dissection, is probably the only way to offer the patient a maximal degree of safety.



FIG. 29 (*Upper*) Gross specimen of a massive diffuse rhabdomyosarcoma involving the vulva and both inguinal regions. (*Lower*) Clinical appearance of patient following vulvectomy and bilateral groin resection of massive rhabdomyosarcoma demonstrated in top figure. (Pack and Eberhart, Surgery 32 1023, 1952.)

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CHAPTER 10

Principles of Amputation for Sarcomas of the Extremities

YORK This fester'd joint cut off, the rest rests sound, This, let alone, will all the rest confound

SHAKESPEARE, *Richard II,* V 3

THE PRINCIPLES governing the choice of amputations for sarcomas of the soft somatic tissues are varied In each individual case there is a constant battle of judgment between the wisdom of the more radical amputation and the need for preservation of an important functional part So many factors interplay here—such as the regional involvement by the tumor, its primary or recurrent status, the histogenesis, the degree of malignancy, its encapsulation or infiltrative method of growth—that no set formulary for management can be established Experience will continue to influence the operator in every circumstance

As knowledge regarding the anatomic and clinical behavior of tumors of the soft somatic tissues increases and as therapeutic experiences, radiologic as well as surgical, in the treatment of cancer of the limbs accumulate, certain definite concepts emerge Perhaps the most significant realization garnered from an unusual experience with malignant tumors of the extremity is that they must be dealt with radically at the outset if there is to be any hope for the patient's survival It has been definitely proved that the prognosis becomes progressively poorer with an increasing number of recurrences following repeated local surgical excisions and conservative amputations, due to an obviously higher incidence of visceral metastasis

Nowhere are these particular groups of cancers more favorably located for the application of radical surgical methods than on the limbs, especially when the regional lymph nodes have already been involved by the cancer Excision and dissection in continuity for radical excision of the primary tumor, intervening lymphatics, and all regional lymph nodes by the same encompassing incision has been described in Chapter 9 If, however, the primary tumor is located too far from the first relay of lymph node metastasis (*e g*, synovial sarcoma of the toe with metastasis to the inguinal lymph nodes), treatment by excision and dissection in continuity is not feasible In such a case, only by exarticulation of the limb combined with excision of the regional lymph nodes can all gross limitations of the cancer be widely removed —interscapulothoracic amputation (with or without supraclavicular neck dissection) for the upper extremity and hip-joint disarticulation (with or without deep iliac dissection) or sacroiliac dis-

articulation (hemipelvectomy) for the lower extremity depending on the clinical and anatomic factors present in the given case

The upper levels of severance must be high if not extreme as related in the sections dealing with fore- and hind quarter amputations The general rule of amputating above the level of origin of the muscle groups involved by the sarcoma is a good principle to observe. The arguments supporting this thesis may be adumbrated as follows

1 The rhabdomyosarcomas may be multicentric and impalpable tumor nodules may exist in superior segments of the muscle, only to grow and be discovered later if the muscle is not entirely removed.
2. Many sarcomas extend imperceptibly high along the muscular and fascial planes
3 The diffuse fascial fibrosarcomas certainly must be removed above the level of the fascial attachment to bone Even to leave the periosteal base at this site increases the hazard of recurrence.
4. Malignant neurilemmomas of the extremities extend high along the nerve sheaths and with the coexistent moniliform beading of the nerve trunks commonly seen in the peripheral manifestations of von Recklinghausen s disease it is difficult at the operating table to be certain of the safe level of amputation[4]
5 Invasion of bone (as distinct from pressure atrophy and necrosis) may result in subperiosteal and intramedullary extension of the sarcoma superiorly and inferiorly therefore amputation through or above the joint with which the affected bone articulates is indicated.

If the sarcoma involves the elbow or necessitates removal of the elbow leaving only a stump of the upper arm the conventional midhumeral amputation or shoulder joint disarticulation should be abandoned, usually in favor of the safer more radical, and only equally crippling interscapulothoracic amputation The arguments for this conclusion are the frequency with which certain malignant tumors of the soft tissues metastasize to axillary lymph nodes the tendency of certain sarcomas (notably the fascial sarcomas or fibrosarcomas and neurosarcomas) to extend centripetally upward along the fascial planes or nerve sheaths and finally the admission of small advantage in possessing the stump of the upper arm and shoulder other than the cosmetic one of its serving as a coat hanger An artificial limb in such a case cannot be appended with good function other than to hook and carry We would delete the operation of humeral disarticulation from the category of cancer surgery there is no circumstance in which interscapulothoracic amputation for malignant tumors of the upper extremity is not a better operation

In the case of the lower extremity the various features of the sarcoma and its treatment should be weighed with care More importance is given to the conservation of the upper thigh because even a small stump will permit the comfortable wearing of an artificial limb The ability to walk with a prosthetic extremity is an advantage over hip-joint disarticulation although even after this latter operation some proud patients will persist in wearing a cumbersome artificial leg

The surgeon electing to amputate for a sarcoma of the soft somatic tissues accordingly does not have wide latitude in his choice of the site of amputation. Whereas amputations performed after trauma for infections or circulatory indurations will be done with a consideration for a maximum of functional result this privilege is usually denied the surgeon amputating for a sarcoma. Because of the vicious and unpredictable behavior of many sarcomas it is neces

sary to amputate radically Accordingly, amputations performed upon patients bearing sarcoma are either most radical or, paradoxically, minor and conservative amputations which are essentially extensions of wide local excisions Minor amputations are performed usually for certain sarcomas of low-grade malignancy which, because of their location (the hands and feet), are so inexplicably intermingled with the normal soft tissues and so often encroach upon bone that a conservative, limited amputation must be performed in order to remove the entire disease Certain principles of amputation emerge from a study of the anatomic behavior of certain sarcomas and from an evaluation of the objectives obtained from a functional standpoint of certain types of amputations.

In considering an amputation it is essential first to consider the patient as a human being subjected to a tremendously traumatic ordeal The problem of rehabilitation and prosthesis must be considered at the time the decision is made to amputate Inasmuch as many cures are being obtained with the proper use of amputations early in the course of a given sarcoma, it is necessary to think in terms of long-term adjustment for the patient. Kessler has divided the rehabilitation program of patients subjected to amputation into four phases. (1) the psychologic attitude of the patient, (2) the technical aspects of the amputation to afford the patient the maximum rehabilitation (as mentioned previously, this choice seldom exists for the surgeon amputating for sarcoma), (3) the proper after-care of the stump, and (4) the proper application and training in the use of prosthetic devices

A consideration of various amputations will be briefly presented.

AMPUTATIONS OF THE LOWER EXTREMITIES

Foot

In considering limited amputations of the foot, one must bear in mind that a retention of the arch of the foot will permit the utilization of the foot for weight-bearing and walking If the amputation can be performed with retention of the tarsometatarsal joints, it will permit weight-bearing, locomotion, and satisfactory muscle balance A transmetatarsal amputation is satisfactory from a functional standpoint, and the patient may wear ordinary shoes bulked with cotton

Lisfranc We do not subscribe to this tarsometatarsal amputation and seldom use it, because the preserved tissues supply an unsatisfactory stump with difficult prosthetic problems

Chopart Amputation This amputation through the astragaloscaphoid joint is also considered unsatisfactory, because the rotation of the os calcis with contracture of the tendo achillis and the resultant equinus deformity make for a most unsatisfactory stump

Pirogoff Amputation This is seldom indicated for cancer in that it aims to preserve the function of the os calcis with the overlying soft tissues of the heel by resecting the tibia and fibula at the supramalleolar level The preserved os calcis is then attached to the tibia and fibula This permits good weight-bearing It is obvious that when the amputation is done for cancer, it would be prohibitive in most cases to preserve the heel

Syme Amputation This supramalleolar resection of the tibia and fibula is a common amputation of the foot Its disadvantage for the cancer operation is again the retention of the skin of the heel region, and it makes for a rather difficult and cumbersome prosthesis at the ankle joint

Below-knee Amputation The ideal

site for an amputation *below the knee* is a point about six inches below the knee, which allows for good blood supply and muscular control

Disarticulation of the Knee This amputation is indicated only in the very young patient so that the epiphysis of the femur is retained for growth. It also may be used for bilateral amputation because it will bear weight well.

The Stokes Gritti Amputation. This operation, in which the femur is resected where the condyles flare and the patella is cut in its horizontal plane and attached to the fixed end of the femur makes for a desirable stump

Amputation at Junction of Lower and Middle Thirds of Femur The classic amputation at the junction of the lower and middle thirds of the femur permits an excellent stump with good muscular control, good leverage and adequate circulation. The stump is a satisfactory one for the fitting of prosthesis

The radical operations of *hip-joint disarticulation* associated with lymph node dissection and *hemipelvectomy* are discussed in more detail in separate chapters devoted to this type of amputation so useful for cancer

AMPUTATIONS OF THE UPPER EXTREMITIES

Hand

It is essential to bear in mind that retention of any of the fingers will be most rewarding to the patient. Even the retention of two fingers will permit good function. Accordingly when an amputation is of the type which represents an extension of a wide local excision, then preservation of any of the fingers and, of course, the thumb whenever possible, is indicated

Conservative Amputations

Amputation at the wrist offers the patient very little function and presents difficulty in the fitting of prosthesis

An amputation above the wrist may be made at the site of election because the kineplasty so highly developed by Kessler is applicable The kineplastic use of the biceps muscles is indicated for amputation made just below the elbow For amputations just above the elbow the use of the pectoralis muscle for kineplastic control of arm prosthesis is available. When amputations are made immediately above the wrist the Krukenberg operation has certain advantages However as mentioned previously these amputations seldom have a place in the surgical treatment of sarcomas

The Tikhor Linberg resection of the upper extremity is rarely indicated for sarcomas of the soft somatic tissues but at times it may be used

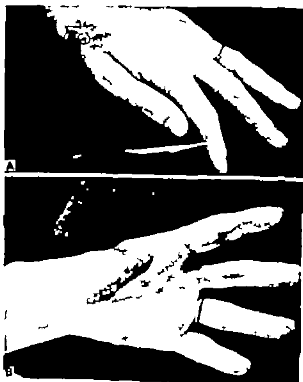


Fig. 30. A. Synovial sarcoma of base of left thumb. *B* After amputation of thumb and corresponding metacarpal bone Eleven years later there was no evidence of local recurrence. (Pack and Ariel, Surgery 28 1047 1950)





FIG 31 *A* Synovial sarcoma involving dorsum of left hand *B* Hand following partial amputation of two digits and corresponding metacarpal bones A functional hand

TIKHOR-LINBERG RESECTION OF THE SHOULDER GIRDLE

This operation encompasses total scapulectomy, partial or complete excision of the clavicle, and resection of the head and neck of the humerus with preservation of the arm, brachial plexus, and subclavian artery and vein

The operation was first planned by the Russian surgeon Tikhor and applied afterward by Bauman and Linberg at the turn of the century The purpose of the operation was threefold (1) as a preferable method of treating certain tumors of the shoulder when the patient refused amputation, (2) for certain cancers or even unusual destuctive inflammatory or traumatic disease when the neurovascular bundle was intact, and (3) for the preservation of an upper extremity capable of limited, but valuable, function

TECHNIC OF THE OPERATION

A racket incision is made along the anterior surface of the clavicle and extended laterally over the deltoid muscle at a distance of 1 to 3 inches down the arm The removal of the clavicle allows an adequate exposure of the subclavian vessels and brachial plexus, ensuring their careful preservation It also makes possible the ligation of the blood vessels prior to resection of the scapula and head of the humerus Division of the pectoral muscles permits a meticulous dissection of the brachial plexus and subclavian vessels The deltoid muscle is transected at its attachments to the clavicle, acromion process, and spine of the scapula The transverse cervical and suprascapular arteries are located, ligated, and severed The long and short heads of the triceps muscle are severed at their insertions The humerus is then transected at or below the surgical neck The posterior incision is carried over the scapula, the trapezius muscle is removed from the spine of the scapula, the levator scapulae rhomboid major and minor muscles are removed medially, and the scapula is raised The teres major muscle and the long head of the triceps are resected, and the specimen is removed The biceps and triceps muscles are sutured anteriorly and posteriorly to the intercostal muscles and anchored to the

periosteum of the ribs The remaining soft tissues and skin are apposed and sutured in the conventional manner

Indications for the Tikhor Linberg Operation

Scapulectomy alone as described by Syme in 1864, is still performed occasionally and then usually for primary bone tumors such as chondrosarcoma De Nancrede in a comprehensive review written in 1909 commented on the inferior end results of scapulectomy for malignant tumors Metastatic cancer in the scapula is infrequent (5 in 5 734 cases reported by Geschickter and Maseritz) and a solitary metastasis almost never occurs Radiation therapy is usually preferable to surgical extirpation for these lesions Resection of the head of the humerus because of its proximity and functional relationship to this region causes no great postoperative problems and the original disease cancer or otherwise, may involve this bone segment itself

The Tikhor Linberg operation has received very little discussion in medical literature because of the limitations of

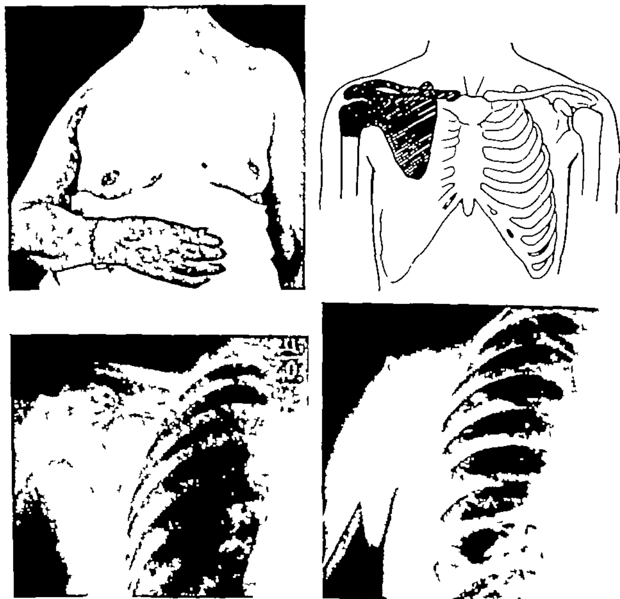


Fig. 32. Tikhor Linberg amputation. (*Top left*) Deformity after resection of clavicle, scapula head of humerus, and shoulder joint. (*Top right*) Schematic outline to show osseous structures sacrificed in the operation (*Bottom left*) Preoperative roentgenogram illustrating destruction of scapula. (*Bottom right*) Postoperative roentgenogram. (Pack and Baldwin Surgery 38 753, 1955)

its use A study of published case reports of this operation lends support to the belief that it is chiefly palliative, because the patients who have not died have often required subsequent and more radical operations for recurrences The only alternative for the Tikhor-Linberg operation is the interscapulothoracic amputation

Some of the lesions involving the shoulder girdle which might furnish indications for the Tikhor-Linberg shoulder girdle resection are

1 *Inflammatory, suppurative diseases* These diseases are associated with massive bone necrosis, multiple fistulas, joint destruction, sepsis, etc Since the introduction of antibiotics, this indication must have become quite infrequent

2 *Metastases to shoulder girdle* Crippling destructive metastases to bone constituting postirradiation failures If the patient would otherwise be expected to have a comfortable life expectancy, this operation might well be used more frequently as a palliative measure

3 *Bone tumors* These tumors are osteogenic sarcoma and chondrosarcoma of scapula invading soft tissues and joint components and unsuitable for scapulectomy We cannot conceive of a situation in which the radiosensitive endothelial myeloma would qualify for an operation of this character

4 *Synovial sarcoma (malignant synovioma)* Although this tumor is not of frequent occurrence around the shoulder joint, it theoretically would be the most suitable of all soft part sarcomas for this specific operation

5 *Liposarcoma* The operation would generally be contraindicated for this tumor Liposarcomas are most frequent in the shoulder and pelvic girdles but seldom compromise bone, they have some degree of radiosensitivity and require extensive sacrifice of soft tissues

6 *Rhabdomyosarcoma* This tumor would seldom be suitable for the Tikhor-Linberg operation because it usually does not involve bone, it may be multicentric in origin, and experience has shown that a fundamental law governing its surgical treatment is to excise all of the muscle groups involved, from origin to insertion, or to amputate proximal to the origin of the muscle groups

7 *Fibrosarcoma* This tumor is commonly diffuse and invasive and may produce a local condition in the shoulder girdle which will tempt the surgeon to perform the Tikhor-Linberg operation and preserve the arm Opposed to this consideration is the pernicious tendency of this sarcoma to extend widely up and down along the fascial planes far beyond the scope of the usual conservative operations

8 *Malignant neurilemmoma* This tumor may invade bone or erode it by continuity, it can be pseudoencapsulated or invasive Two hazards, namely, involvement of the brachial plexus and the predisposition for recurrence proximally along the nerve trunks, may render it unsuitable for this operation

9 *Deeply invasive cancers of the skin* Epidermoid carcinomas of the skin of the shoulder may involve the bones and shoulder joint As in our case (Fig 32), they may have recurred after attempts at radiation therapy and are sometimes associated with radiation fibrosis and ulceration, necrosis, suppuration, fixation of joint, intractable pain, and disability

At the completion of the operation, the lower arm, forearm, and hand are intact, the functions of the forearm and hand are largely retained but, of course, shoulder and upper arm movements are no longer possible The forearm maintains its function and utility completely, with the carrying angle being maintained without difficulty. As previously stated, the boneless upper portion of the arm is fixed by suturing it to the chest wall, after complete healing, followed by training of the arm, some carrying may be done but, of necessity, with limitation

as to weight in comparison with the normal arm. To use this arm above the horizontal, it is necessary to use the other arm for support, but it can be raised for such functions as combing the hair without discomfort. The cosmetic results are such that a good tailor or the use of a properly fitting prosthesis can build up the shoulder for the proper wearing of clothes

The actual indications for the Tikhor Linberg operation must be quite infrequent as we have employed it only once during a considerable experience with major amputations, that is, interscapulothoracic amputation in 88 cases hip-joint disarticulation in 94 cases, and interilioabdominal amputation (hemipelvectomy) in 46 cases [G T P]

RADICAL AMPUTATION

Of the various amputation technics for treating extensive cancers of the extremities, disarticulation of the entire limb gives promise of becoming the most effective

Disarticulation of the shoulder joint is a well recognized operation which is resorted to more often for traumatic, infectious, and other nonneoplastic conditions and will not be considered in this study Hip-joint disarticulation, although less frequently employed, is of distinct value in the treatment of malignant tumors The surgical principle of exarticulation of an extremity with excision of the regional lymph nodes for malignant tumors will be presented.

More rarely the shoulder girdle (interscapulothoracic amputation) or the buttock and corresponding innominate bone (sacroiliac disarticulation) must be included in the amputation if a tumor is to be completely removed. Some of these operations have been performed for palliative purposes only because many of the patients harbored extensive and hopelessly advanced cancers It will be shown that palliation and comfort and sometimes a cure may be anticipated by employing these relatively safe surgical procedures

REHABILITATION AND PROSTHESIS AFTER AMPUTATION

When considering the functional usability of the stump one may regard the use of the stump of an amputation of a lower extremity as essentially for weight bearing and locomotion. When one tries to adjust a prosthesis to duplicate the function of the upper extremity it becomes an impossibility because the functions of the upper extremity are so great that at best the prosthesis acts as an extremely poor imitation. Kessler states "The hand is not only a tool, but it is a sensory organ. It is the eye of the blind and the tongue of the mute It is more than that it is an extension of man's brain Through it he has achieved his high place in the animal kingdom" Inasmuch as the prosthetic device for amputations of the upper extremity seldom accomplishes good reduplication of function except in limited instances the thought of retaining this function should be dismissed from the surgeon's mind in amputating for sarcoma, for as has been pointed out, the operative demands are so great that it is usually necessary to perform only the most radical types of upper extremity amputations for sarcomas

The preparation for a prosthesis after a given amputation begins with the stump There is at first a general fibrosis of the stump with an edematous appearance, after which atrophy of the entire stump occurs. This atrophy is unpredictable and irregular and makes it diffi

cult to determine how a given stump will behave. Some will atrophy very rapidly and remain stationary, while others will remain apparently edematous for months and even years, after which atrophy will begin. It is of the utmost urgency that close measurements be made of the stump and that every effort be made to keep the stump (especially one of a lower extremity) in the form of a cone so that a proper prosthesis may be fitted. This is accomplished by constant application of elastic bandaging to the stump, attempting to mold the stump to the desired form and to apply enough pressure to enhance the normal shrinkage of the stump. Another necessity in the postoperative care of the stump is the prevention of contractures. This is accomplished by proper exercises of the stump during the immediate postoperative phase. Any painful neuromas should be treated at this time. The type of prosthesis will be determined by the level of amputation, which has been discussed in preceding paragraphs. It is emphasized that constant measurements of changes of the stump by an intelligent well-trained limb-fitter will aid greatly in assisting the amputee to rehabilitation.

Careful and prolonged training is another necessity when the stump has been fitted. This can only be accomplished by an intelligently planned course of training by personnel equipped by education and preference for this type of work. Prostheses for the radical amputations of the lower extremities (the hip-joint disarticulation or hemipelvectomy) are available although not too satisfactory. Some patients, however, adjust very nicely and prefer them (Fig. 33).

Prostheses for an upper extremity, in contrast to a lower extremity, must be made to suit the patient. His profession will also determine the type of prostheses to be utilized. The following list, based on Kessler's ideas, represents the different types available.

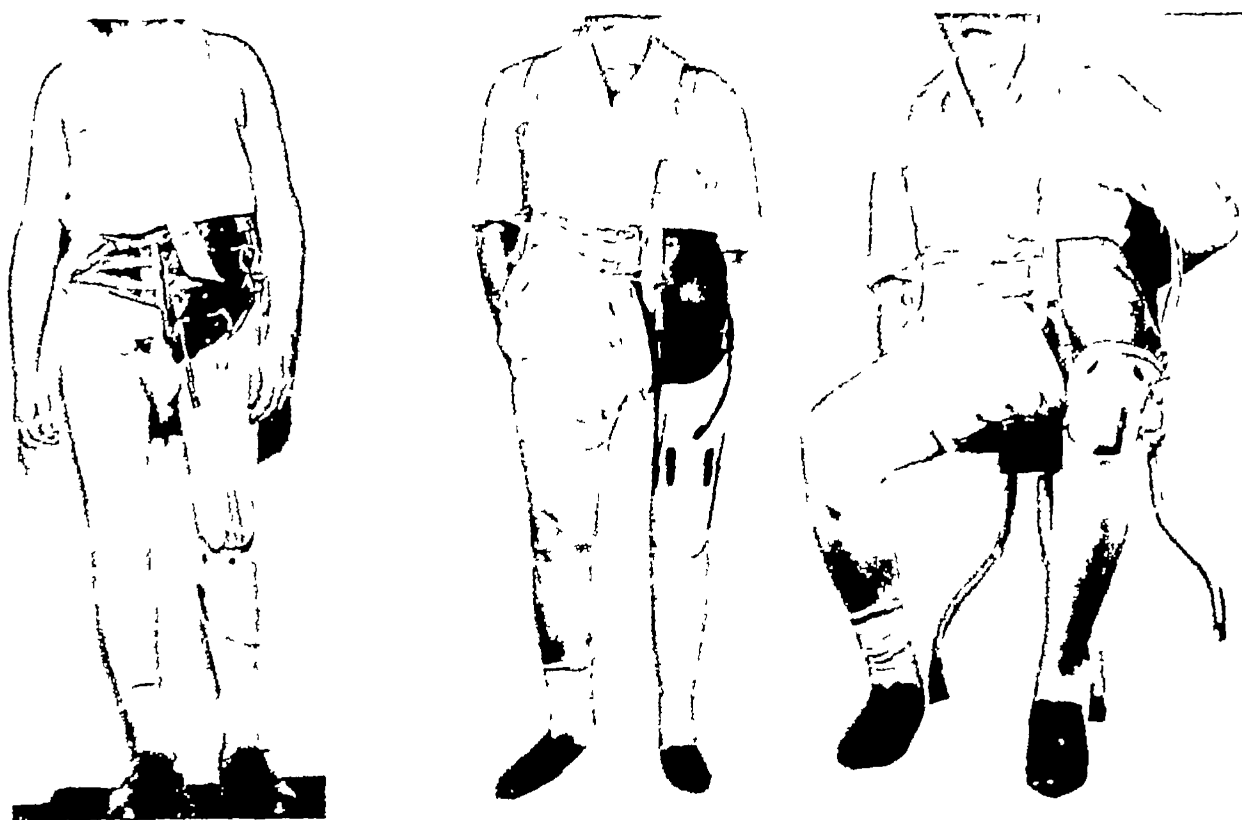


Fig. 33. Photographs showing prostheses utilized for hip-joint disarticulation and hemipelvectomy and illustrating adaptability of the prostheses. Note the similarity of construction of the prostheses for hemipelvectomy and hip-joint disarticulation. (Pack and Ehrlich, Ann. Surg. *123*:965, 1946. *Courtesy* J. B. Lippincott Company.)

1 No prosthesis
2 Dress hands (plastic, felt, wool or rubber)
3 Functional prosthesis
   a Solid hook
   b Utility hook (operated by control cord from shoulder)
   c Mechanical hand (interchangeable with utility hook and operated in the same manner)
   d Special mechanical hand (with multiple articulation of the Carnes type)
   e Electrical arm (now in experimental stage)
4 Kineplasty
5 Krukenberg operation

In the cineplasty the muscular motors which are attached to operate the prosthesis are fashioned in the amputation stump In the Krukenberg procedure the forearm stump is split longitudinally to provide two long opposing edges for prehensile ability

Most of the prostheses for the upper extremity are unsatisfactory and not suited to patients operated upon for cancer Although it is theoretically possible to use a mechanical prosthesis for a scapulothoracic amputation it is used only in the unusual case in which the weight of the apparatus the extent of harnessing, and the tedious efforts of training can be borne by the patient The most satisfactory appliance for the most part is one which attempts to replace the contour of the shoulder to permit the patient to wear normal clothes This is accomplished by a plastic type of mold to fill the shoulder defect

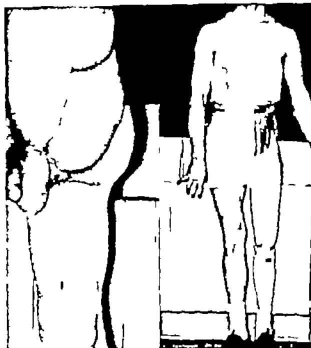


Fig 34 Interilioabdominal amputation (hemipelvectomy) for rhabdomyosarcoma. Prosthesis for patient after hemipelvectomy for rhabdomyosarcoma (Pack and Eberhart Surgery 32 1023 1952.)

END RESULTS OF MAJOR EXARTICULATIONS FOR MALIGNANT TUMORS OF THE EXTREMITIES

Accomplishments obtained by the use of radical amputations in treating sarcomas of the extremities will be presented and causes of failures analyzed. Total experience with the radical amputations is presented so that comparison can be made of results obtained by these procedures in treating sarcomas with results in other neoplasms

The radical exarticulations have been done more frequently for soft part sarcomas next for malignant tumors of the skin, and least frequently for bone sarcomas The percentages follow

Interscapulothoracic amputation

1 Soft tissue sarcomas 53 per cent
2 Skin 37 per cent
3 Bone, 9 per cent

Hip-joint disarticulation

1 Soft tissue sarcomas 44 per cent
2 Skin 46 per cent
3 Bone, 11 per cent

Interilioabdominal amputation

1 Soft tissue sarcomas 56 per cent
2 Skin 24 per cent
3 Bone 20 per cent

These figures are not in proportion to the natural frequency of these neoplasms, inasmuch as skin cancers, *i e*, epitheliomas and melanomas, are common, soft somatic sarcomas less frequent, and malignant bone tumors rarest of all

Causes of Failure after Major Exarticulations

An analytical survey of 228 amputations reveals certain causes of failure

1 Whenever the primary cancer was situated other than on the amputated extremity, the result could only be palliative (seven cases)

2 Borderline operability of the malignant tumor These amputations have often been operations of desperation

3 Many of the exarticulations were performed for recurrent cancer The prognosis is 15 to 45 per cent superior when the same operations are applied as the primary or initial treatment

4 Recurrence in the stump Malignant tumors which extend insidiously upward along fascial and intermuscular planes and nerve sheaths may recur in the stump even after the highest amputations Specifically such tumors include fibrosarcoma, synovioma, and neurilemmoma The chondrosarcomas seldom recur locally after forequarter amputations, but when originating in the os innominatum, they may recur in the pubis or sacrum after hemipelvectomy

5 Distant metastases Metastases to the lungs are detected sometimes months or years after the operation, especially in the case of osteosarcoma, rhabdomyosarcoma, malignant synovioma, melanoma, and liposarcoma The liposarcomas and melanomas not infrequently metastasize to the heart and brain

Determinate Five-year Cures

In a breakdown of the curability based on patients treated more than five years previously, the over-all cures for all cancer types are. hip-joint disarticulation, 15 4 per cent, interscapulothoracic amputation, 33 3 per cent, and hemipelvectomy, 21 4 per cent For soft part sarcomas the five-year-cure rates following hip-joint disarticulation, interscapulothoracic amputation, and hemipelvectomy are, respectively 13 3 per cent, 39 3 per cent, and 10 0 per cent

Histories show the following 5-year-cure rate for malignant tumors of varied histogenesis

1 *Malignant melanoma* Four patients living and well of whom 3 had hip-joint disarticulations and 1 had interscapulothoracic amputation

2 *Metastasizing epidermoid carcinoma* Two patients living and well, 1 following hip-joint disarticulation and 1 after interscapulothoracic amputation

3 *Reticulum-cell sarcoma* One patient living and well after forequarter resection This is unusual in view of the tendency of this tumor to become generalized

4 *Malignant neurilemomma* Five of the 16 exarticulations resulted in 5-year cures (31 per cent) Four of these 5 patients were well for more than 10 years

5 *Chondrosarcoma* Of the 11 patients undergoing amputation, 5 are living, 2 over 5 years, both having had hemipelvectomy

6 *Osteogenic sarcoma* Of 9 patients, 3 are living and well, all less than 5 years

7 *Rhabdomyosarcoma* Twenty-four patients of whom 6 are living and well, 5 of them less than 5 years One patient is well more than 10 years

8 *Angiosarcoma* Five patients of whom 1 is living and well more than 5 years

9 *Malignant synovioma* Fourteen patients of whom only 2 are living and well, 1 more than 5 years

10 *Skin cancers—primary site elsewhere than on an extremity.* Seven patients, none of whom was cured The

average postoperative length of life was 12 months Three patients with breast cancers had interscapulothoracic amputation in conjunction with radical mastectomy One patient requiring amputation for metastatic colonic cancer survived for 22 months

Influence of Previous Unsuccessful Treatment on the End Results of Exarticulation

Previous attempts at therapy by surgical dissection, irradiation, or lesser amputations unfavorably influence the results achieved by the three types of major amputations for residual cancers Of patients undergoing interscapulothoracic amputation, 37 per cent of those having no previous treatment and 33 per cent of those having recurrent or residual cancers were living and well. Of patients undergoing hip-joint disarticulation, 42 per cent of those having no previous treatment and 30 per cent of those having recurrent or residual cancers were living and well. Of patients undergoing hemipelvectomy 42 per cent of those having no previous treatment and 29 per cent of those having recurrent or residual cancers were living and well

Operative Mortality

There were no operative deaths as the result of the 228 major exarticulations

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CHAPTER 11

Hip-joint Disarticulation*

EARLY HISTORY

AMPUTATION through the hip joint is an operation that even now is not undertaken lightly In the early years of the last century when sepsis attacked almost every wound and anesthesia was unknown, it must have demanded more than ordinary courage for both surgeon and patient Amputation through the hip joint was first successfully performed by Walter Brachear of Bardstown Kentucky in August, 1806 for a comminuted compound, multiple fracture of the femur in a 17 year-old mulatto slave boy A midthigh amputation was done, at which time the major vessels were ligated The bone was then exposed up to the head of the femur on the outer aspect of the thigh, and the head of the femur was disarticulated—all of this without anesthesia or antiseptics Brachear never published an account of his operation

The earliest recorded instance of a well-conceived surgical amputation through the hip joint was that of Sir Astley Cooper The operation was performed at Guy's Hospital on January 16 1824 The patient was a 40-year-old white male whose limb had been amputated just above the knee some years before The femur had "become diseased from the extremity of the stump to the trochanter major" The actual removal of the limb took 20 minutes and the ligation of the major vessels and application of a dressing 15 minutes more The patient became faint during the operation but revived on the administration of wine and admission of fresh air He bore the operation with extraordinary fortitude After it was completed, he said to Cooper that it was the hardest day's work he had ever gone through, to

TABLE 6 HIP JOINT DISARTICULATION INCIDENCE ACCORDING TO HISTOLOGIC TYPE OF TUMOR

Histologic Type of Tumor	*Number*	*Per cent age*
Total cases	94	100 0
Tumors of skin—*Total*	43	45 7
Melanoma	41	43 6
Carcinoma	2	2 1
Tumors of soft somatic tissues—*Total*	41	43 6
Sarcoma unclassified	15	16 0
Malignant neurilemmoma	7	7 4
Rhabdomyosarcoma	5	5 3
Fibrosarcoma	5	5 3
Synovioma	5	5 3
Liposarcoma	3	3 2
Reticulum-cell sarcoma	1	1 1
Tumors of bone—*Total*	10	10 6
Chondrosarcoma	3	3 2
Osteogenic sarcoma	4	4 2
Endothelial myeloma	2	2 1
Periosteal fibrosarcoma	1	1 1

* In collaboration with Harry E. Ehrlich.

which Sir Astley replied that it, too, was almost the hardest he had ever experienced.

The final note on this historic case is as follows. "August, 1825 This patient perfectly recovered, and is now living at the country residence of Sir Astley Cooper"

Many of the early hip-joint disarticulations were performed by such famous surgeons as Billroth, Trendelenburg, McBurney, Wyeth, Senn, and Halstead.

INDICATIONS FOR AMPUTATION THROUGH THE HIP JOINT

Large malignant tumors of the soft somatic tissues of the middle and upper thigh which cannot be completely removed by wide local excision and for which a high thigh amputation cannot assure an adequate margin are best treated by hip-joint disarticulation When the lower extremity is the seat of a bulky, ulcerated, infected, foul-smelling tumor which involves the upper thigh (malignant lymphoma, Kaposi's hemorrhagic sarcoma, primary malignant tumor with distant metastasis, and metastatic carcinoma) and the patient's general condition has not deteriorated too much, amputation through the hip joint for palliation and comfort is occasionally justified Elimination of sepsis and pain, and conversion to ambulation and partial activity can only be accomplished in hopelessly advanced cases by radical amputation If exarticulation of the hip joint is performed for either a primary operable malignant tumor or for palliative purposes only, it is requisite that the neoplastic process does not extend to or through the hip joint, otherwise nothing less than amputation through the sacroiliac joint will suffice

For malignant melanoma of the skin of the lower limb in which involved inguinal and femoral lymph nodes are far removed from the primary tumor, the principle of "excision and dissection in continuity" cannot be applied Under such circumstances only hip-joint disarticulation combined with radical groin dissection will accomplish effective removal of the primary tumor, intervening lymphatics, and all surgically accessible lymph nodes Such a combination of surgical procedures will be discussed in a separate section of this report

Malignant tumors of bone and periosteum which occur in the upper and middle femur and for which high thigh amputation cannot assure an adequate margin should be treated by hip-joint disarticulation, provided the hip joint and contiguous structures are not involved by tumor Endothelial myeloma in such a location should be similarly treated if exhaustive studies have demonstrated absence of this disease elsewhere

TABLE 7 HIP-JOINT DISARTICULATION SEX AND AGE OF PATIENTS

Type of Malignant Tumor	*Total*	*Male*	*Female*	*Youngest Patient*	*Oldest Patient*
Total	94	45	49	3 yr, male	72 yr, male
Tumors of skin	43	19	24	16 yr, male	65 yr, 1 male 1 female
Tumors of soft somatic tissues	41	21	20	3 yr, male (sarcoma, unclassified)	72 yr, male (reticulum-cell sarcoma)
Tumors of bone	10	5	5	7 yr male (osteogenic sarcoma)	62 yr, male (chondromyxosarcoma)

Neoplasms which extend high up on the thigh and which are destined to undergo malignant transformation, such as a huge plexiform neurofibroma (histologically containing atypical foci) in cases of multiple cartilaginous exostoses, are best treated by removal of the extremity through the hip joint, provided they cannot be excised completely by a more conservative operation

PREOPERATIVE CONSIDERATIONS

The amount of blood which is contained in one of the lower limbs, even after ligation of the common femoral artery, is considerable Unfortunately, no



Fig 36 (*Upper*) Hip-joint disarticulation for recurrent malignant neurilemmoma of sciatic nerve (*Lower*) Note moniliform beading of nerve trunk This recurrent sarcoma was fungating through the skin The patient was bedridden and suffered intractable pain (Pack and Ehrlich Ann Surg *123* 965, 1946 *Courtesy*, J B Lippincott Company)

studies on blood loss estimation were made in any of these cases Despite meticulous hemostasis and minimal apparent blood loss shock of varying degrees will occasionally occur just as the specimen is being detached from the patient if other precautions for the conservation of blood are not taken Shock may here be attributed to a sudden decrease in the circulating volume and can be prevented, for the most part, by constant administration of whole blood during the operation Use of an elastic bandage wrapped around the limb to be amputated is invaluable in conserving circulating blood volume It should be carefully applied several hours before the operation is planned An elastic bandage is definitely contraindicated, however in cases of melanoma, in which it might possibly aid in the dissemination of tumor cells into the blood stream

In the event that the tumor is ulcerated and infected, daily local treatment, consisting of gentle debridement cleansing and antiseptic sprays and frequently applied saline dressings is of distinct value in reducing the septic condition of the limb The incidence of postoperative wound infection in this group of cases was decidedly low

Although vaginal preparation is not as essential as for sacroiliac disarticulation the perineal and operative fields can be rendered surgically cleaner by the use of preoperative cleansing douches and antisepsis of the vaginal tube in the operating room by any of the accepted methods A Foley urethral catheter is inserted into the bladder before the patient is taken to the operating room

OPERATIVE TECHNIC

The patient is placed on the table with the affected thigh slightly abducted and externally rotated In the male the scrotum is temporarily sutured to the opposite thigh, this step adequately removes the genitals from the operative field.

An anterior racquet incision is the approach of choice Obviously the amount of skin to be removed might influence the extent and position of the incision. The upper limit of the incision is placed just above the midportion of Poupart's ligament and continued vertically downward for from 4 to 5 cm The lateral limb of the incision is carried downward and outward across the anterior aspect of the thigh, coursing just above the greater trochanter The medial extension of the incision is similarly carried across the thigh in an opposite direction but at a somewhat higher level, corresponding to a point several centimeters below the genitocrural fold. These incisions are joined posteriorly below the infragluteal

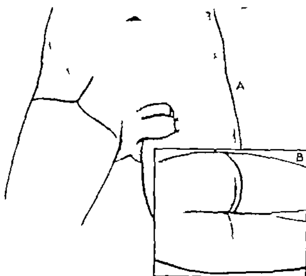


Fig. 37 A. Anterior racquet incision for hip-joint disarticulation. The upper limit of the incision is placed above the midportion of the inguinal ligament and continued vertically downward for from 4 to 5 cm. The lateral limb courses just above the greater trochanter The medial limb is carried across the thigh at a somewhat higher level, several centimeters below the genitocrural fold. *B* These incisions are joined posteriorly below the infragluteal fold The posterior incision comes to lie almost transversely across the thigh. (Pack and Ehrlich Ann. Surg. *123*:965 1946 *Courtesy* J B Lippincott Company)

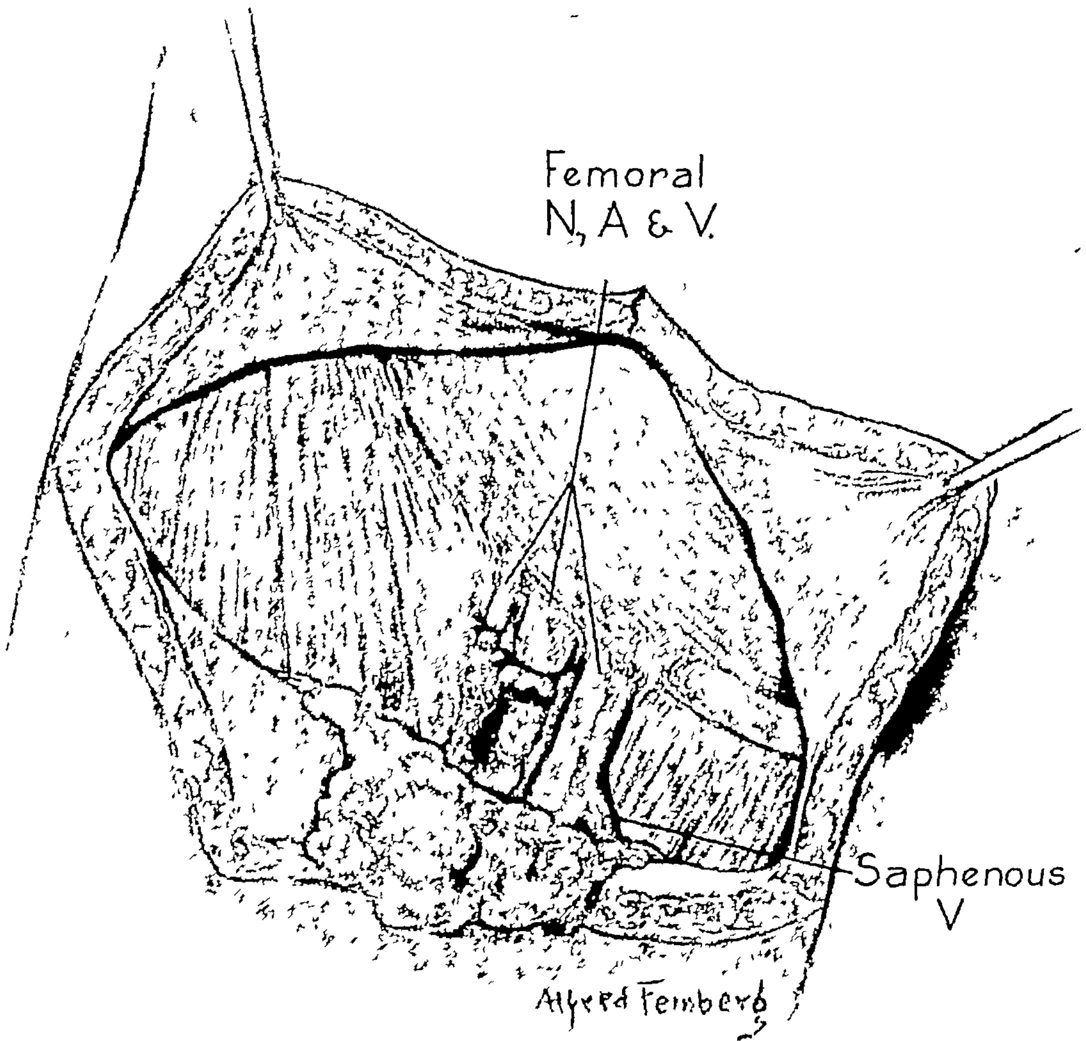


Fig 38 The neuromuscular bundle in Scarpa's triangle has been cleared The femoral artery has been ligated and divided above its profunda branch The femoral nerve has also been transected (Pack and Ehrlich, Ann Surg *123* 965, 1946. *Courtesy,* J B Lippincott Company)

fold The posterior incision comes to lie transversely across the thigh

The apical portion of the incision is deepened through the subcutaneous tissues and fascia, reflecting downward a V-shaped flap The edge of the inguinal ligament is cleared, and the neurovascular bundle is exposed The femoral artery is removed from its sheath, doubly ligated above the profunda femoris, and cut The femoral nerve is delivered and severed

The incisions are deepened through subcutaneous tissues and fascia in their entirety Thick skin flaps are developed medially to the pubes and laterally well above the greater trochanter The anterior femoral group of muscles (sartorius and rectus femoris) is cut ra low so that the muscles may be] used to cover the acetabulum All o muscles are severed as near to thei sertions as possible. The limb is t abducted, and the median femoral gr of muscles (gracilis, pectineus, and ductors) is transected The limb is r adducted, the tensor fasciae latae is t put on a stretch and is severed. ' femoral vein is finely ligated and vided The anterior dissection has n been completed

The limb is again adducted and ternally rotated This maneuver bri the greater trochanter into view so t the muscles which insert into it may severed after which the gluteal mus

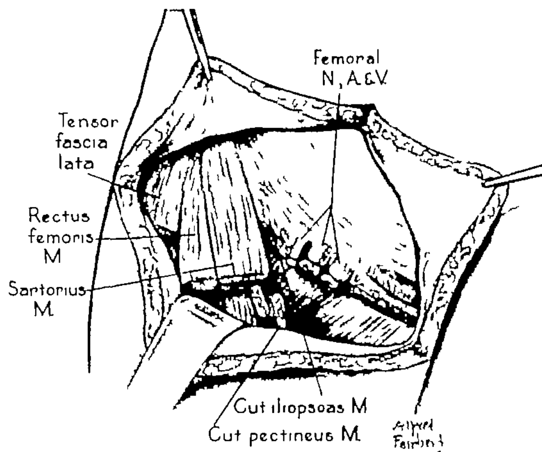


FIG. 39 The anterior and median femoral muscle groups have been transected. The sartorius and rectus femoris muscles are cut rather low so that they may be used later to cover the acetabulum. The femoral vein has been ligated and divided completing the anterior dissection. (Pack and Ehrlich, Ann. Surg 123:965 1946 *Courtesy* J B Lippincott Company)

group (gluteals piriformis obturators quadratus femoris and gamelli) is cut

The capsule of the hip joint is exposed and made taut by vigorously adducting and internally rotating the limb After the capsule of the hip joint is incised further adduction actually forces the head of the femur out of the acetabulum (surgical dislocation) The round ligament is then severed The head of the femur is drawn forward and outward The specimen is now attached to the patient by a posterior pedicle consisting of the hamstring muscles and sciatic nerves These are cut across and the specimen is removed.

The excessive muscular and ligamentous tissues are trimmed. The acetabulum is covered by suturing over the previously prepared muscle flap (sartorius

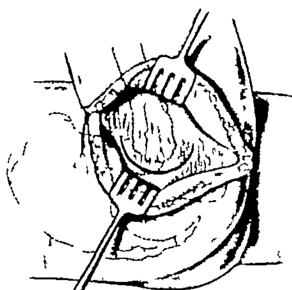


FIG 40 Beginning of posterior dissection. The greater trochanter is brought into view by vigorously adducting and internally rotating the extremity The muscles which insert into it may then be severed (Pack and Ehrlich, Ann Surg. 123:965 1946 *Courtesy* J B Lippincott Company)

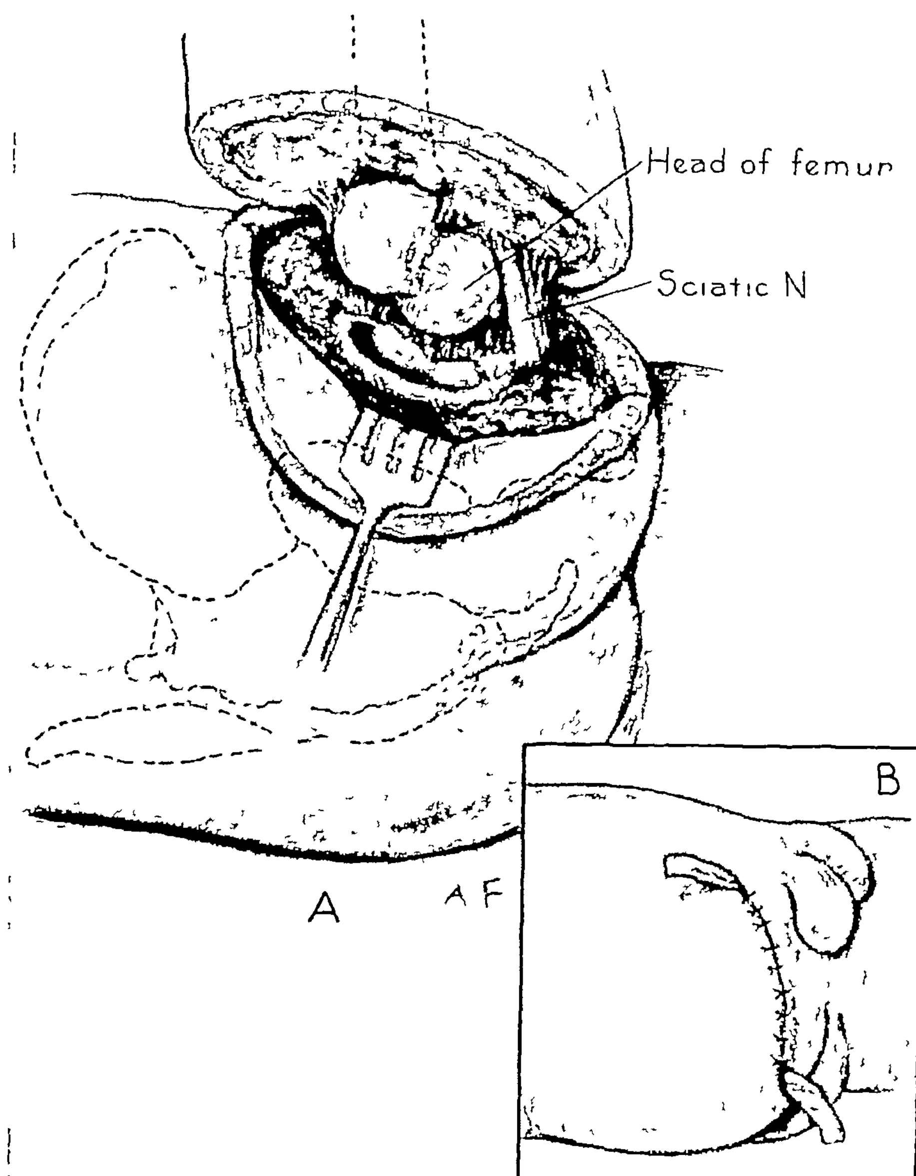


FIG 41 A Posterior dissection continued Median femoral group of muscles has been cut The capsule of the hip joint has been completely incised By further adducting the limb, the head of the femur is forced out of the acetabulum (surgical dislocation) The round ligament has also been severed Specimen is now attached to the patient by a posterior pedicle consisting of sciatic nerves and hamstring muscles *B* Wound closure (Pack and Ehrlich, Ann Surg *123* 965, 1946 *Courtesy,* J B Lippincott Company)

and rectus femoris) The skin flaps are approximated, reshaped if necessary, and closed The wound is appropriately drained

CONTROL OF HEMORRHAGE

Numerous devices, such as Wyeth's pin, Senn's clamp, and others, and several maneuvers, such as preliminary ligation of the common iliac artery and digital compression of the abdominal aorta, have been suggested for the prevention and control of hemorrhage These are unnecessary After secure ligation of the common femoral artery, the main blood supply is satisfactorily controlled Other branches are clamped as cut during the course of the operation The only major vessel which might produce troublesome bleeding is the obturator artery which is easily secured even after it has been cut

TABLE 8 TYPE OF TUMOR AND END RESULTS FOLLOWING HIP-JOINT DISARTICULATION

Type of Malignant Tumor	Total Cases	Patients Who Have Died			Patients Who Are Living				
							Without Cancer		
		Total Cases	With Cancer	Without Cancer	Total Cases	With Cancer	Under 5 Yr	5–10 Yr	Over 10 Yr
Total cases	94*	61	59	2	30	2	22	4	2
Tumors of skin—*Total*	43†	26	25	1	16	2	12	2	0
Melanoma	41†	25	24	1	15	2	11	2	0
Carcinoma	2	1	1	0	1	0	1	0	0
Tumors of soft somatic tissues—*Total*	41	31	30	1	9	0	5	2	2
Sarcoma unclassified	15	14	14	0	1	0	1	0	0
Malignant neurilemmoma	7	4	3	1	3	0	1	0	2
Rhabdomyosarcoma	5†	3	3	0	1	0	1	0	0
Fibrosarcoma	5	2	2	0	3	0	2	1	0
Synovioma	5	5	5	0	0	0	0	0	0
Liposarcoma	3	2	2	0	1	0	0	1	0
Reticulum-cell sarcoma	1	1	1	0	0	0	0	0	0
Tumors of bone—*Total*	10†	4	4	0	5	0	5	0	0
Osteogenic sarcoma	4†	1	1	0	2	0	2	0	0
Chondrosarcoma	3	1	1	0	2	0	2	0	0
Endothelial myeloma	2	2	2	0	0	0	0	0	0
Periosteal fibrosarcoma	1	0	0	0	1	0	1	0	0

* Three patients lost to follow-up
† One patient lost to follow-up

COMPLICATIONS

In general, the course following hip-joint disarticulation is relatively smooth and uneventful. Severe shock and hemorrhage are not encountered. Complications such as anemia, urinary retention and abdominal distention, which not infrequently follow amputation through the sacroiliac joint, do not occur after amputation through the hip joint. The preoperative use of an elastic bandage, delayed ligation of the common femoral vein, administration of blood during the operation, together with meticulous attention to hemostasis contribute in no small measure to the notable absence of complications

The patients are out of bed on the second or third postoperative day Because of the bulky pressure dressing, a retention catheter is placed in the bladder and removed after a lighter dressing is applied (about 48 hours) If the tumor is ulcerated and infected, antibiotic medication is administered for several days postoperatively If the skin flaps are sufficiently thick and all redundant muscle has been removed from the stump wound drainage is not prolonged. Drains are shortened on the fifth and removed on the seventh to ninth postoperative day Frank wound infections are occasionally encountered especially in cases in which the tumor is ulcerated and infected and in which radical groin

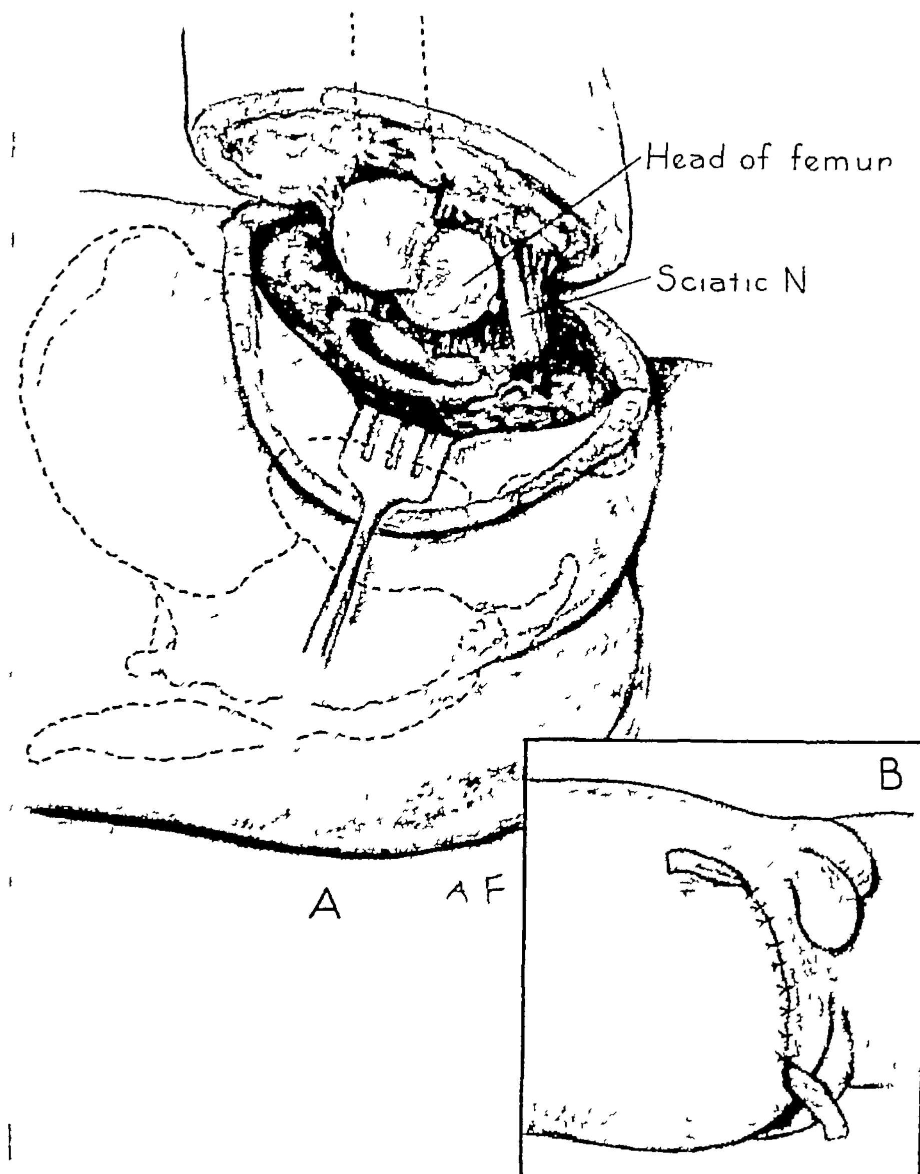


Fig 41 *A* Posterior dissection continued Median femoral group of muscles has been cut The capsule of the hip joint has been completely incised By further adducting the limb, the head of the femur is forced out of the acetabulum (surgical dislocation) The round ligament has also been severed Specimen is now attached to the patient by a posterior pedicle consisting of sciatic nerves and hamstring muscles *B* Wound closure (Pack and Ehrlich, Ann Surg *123* 965, 1946 *Courtesy,* J B Lippincott Company)

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Carcinoma	2	1	1	0	1	0	1	0	0
Tumors of soft somatic tissues—*Total*	41	31	30	1	9	0	5	2	2
Sarcoma, unclassified	15	14	14	0	1	0	1	0	0
Malignant neurilemmoma	7	4	3	1	3	0	1	0	2
Rhabdomyosarcoma	5†	3	3	0	1	0	1	0	0
Fibrosarcoma	5	2	2	0	3	0	2	1	0
Synovioma	5	5	5	0	0	0	0	0	0
Liposarcoma	3	2	2	0	1	0	0	1	0
Reticulum-cell sarcoma	1	1	1	0	0	0	0	0	0
Tumors of bone—*Total*	10†	4	4	0	5	0	5	0	0
Osteogenic sarcoma	4†	1	1	0	2	0	2	0	0
Chondrosarcoma	3	1	1	0	2	0	2	0	0
Endothelial myeloma	2	2	2	0	0	0	0	0	0
Periosteal fibrosarcoma	1	0	0	0	1	0	1	0	0

Three patients lost to follow up
† One patient lost to follow-up

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TABLE 9 PREVIOUS TREATMENT IN RELATION TO END RESULTS AFTER HIP-JOINT DISARTICULATION

(The Memorial Center and the Pack Medical Group)

Type of Previous Treatment	*All Cases*			*Tumors of Skin*			*Tumors of Soft Somatic Tissues*			*Tumors of Bone*		
	Total	*Died*	*Living*	*Total*	*Died*	*Living*	*Total*	*Died*	*Living*	*Total*	*Died*	*Living*
Total cases	94*	60	31	43†	26	16	41†	30	10	10†	4	5
No previous treatment	19†	10	8	7	5	2	7	5	2	5†	0	4
Irradiation only	6	5	1	0	0	0	4	3	1	2	2	0
Excision‡	43†	30	12	14	7	7	26†	21	4	3	2	1
Dissection§	11	7	4	10	6	4	1	1	0	0	0	0
Amputation‖	15†	8	6	12†	8	3	3	0	3	0	0	0

* Three cases lost to follow-up
† One case lost to follow-up
‡ Excision only 29
Excision and irradiation 14
§ Dissection only 2
Dissection and excision 7
Dissection, excision, and irradiation 2
‖ Amputation only 6
Amputation and excision 4
Amputation, excision, and irradiation 1
Amputation and dissection 1
Amputation, excision, and dissection 1
Amputation and irradiation 1
Amputation, excision, dissection, and irradiation 1

dissection accompanies amputation In most cases, however, healing occurred per primam

As with amputations elsewhere, stump pain and phantom limb symptoms are not infrequently distressing postoperative complications

Anemia, which is almost a constant postsurgical manifestation of sacroiliac disarticulation, does not occur following *amputation through the hip joint* The loss of active bone marrow following hip-joint disarticulation is not sufficient to interfere significantly with hemopoiesis, but the amount of additional marrow contained in the innominate bone might be such that its loss, together with that contained within the long bones of the lower limb, probably results in a resistant but temporary anemia. The anemia which complicates the course of patients subjected to amputation through the sacroiliac joint will be *further discussed in a subsequent section* of the present report

HIP-JOINT DISARTICULATION COMBINED WITH DEEP ILIAC DISSECTION—SURGICAL PRINCIPLES AND INDICATIONS

In the treatment of sarcoma of the extremities with demonstrable involvement of the regional lymph nodes, the principle of excision and dissection in continuity should be practiced whenever possible If the primary tumor is located too far from the first relay of lymph node metastasis, this surgical principle cannot, of course, be employed In such cases wide surgical excision of the primary lesion, subsequently followed by a separate dissection of the regional lymph nodes, will only very rarely succeed in removing the intervening lymphatic pathways between the primary tumor and the involved regional lymph nodes,

making local recurrence of distant metastasis almost inevitable This conclusion has been reached after many years of surgical experience with over 700 cases of sarcoma. In those cases, therefore in which it is technically impossible to excise the primary tumor with sufficient width together with the intervening lymphatics and involved regional lymph nodes by excision and dissection in continuity exarticulation of the limb together with removal of the lymphatic contents of the regional node-bearing space (groin and retroperitoneal space) is indicated—interscapulothoracic amputation and supraclavicular dissection for the upper extremity and hip-joint disarticulation combined with deep iliac dissection for the lower limb

Other highly malignant neoplasms such as spindle-cell carcinoma, melanoma, and endothelial myeloma, may not infrequently metastasize to the regional lymph nodes The same surgical principles should be applied for their management as for sarcoma.

Operative Technic

The preoperative preparation, anesthesia, and other considerations are the same as for amputation through the hip joint. Bladder catheterization should always be done. Since this combined operation is usually performed for malignant tumors, an elastic bandage is not usually applied for it might possibly disseminate tumor cells into the blood stream. The technic of radical groin dissection is employed but is altered by omitting the dissection of the upper thigh and Hunter's canal With this combined operation, a deep iliac dissection is performed, and the groin space is actually excised rather than dissected.

An anterior racquet incision is made as

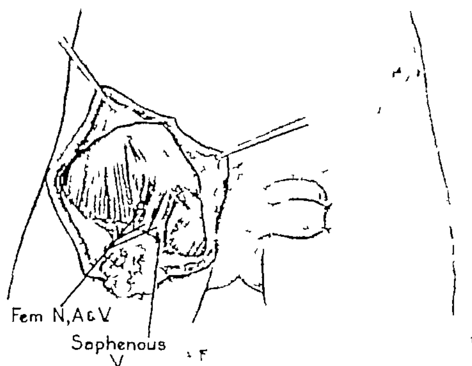


Fig 42. Hip-joint disarticulation combined with deep iliac dissection. After development of anterior flaps, the lower anterior abdominal wall, inguinal ligament, inguinal canal, and Scarpa's triangle are cleared of all fascial, fatty areolar and lymphatic tissues; this bulk of tissue is dissected downward and is left attached to the specimen The femoral vessels and nerve may be seen exposed and cleared. First stage of groin dissection completed. (Pack and Ehrlich, Ann. Surg. 123:965 1946 *Courtesy* J B Lippincott Company)

for hip-joint disarticulation but is so modified that the upper extremity of the incision is placed from 4 to 5 cm above and from 3 to 4 cm medial to the anterior superior iliac spine The apex of the incision lies above the junction of the outer and middle thirds of Poupart's ligament The anterior portions of the medial and lateral flaps are developed The skin edges are defined by the scalpel, and towels are applied to the wound edges by means of numerous tenacula These tenacula are very helpful in facilitating subsequent dissection of fat and fascia from the skin, because when dealing with sarcoma, it is important to make the flaps thin With the tenacula elevated, the subcutaneous fat is dissected widely until the inguinal region and lower abdominal wall over the iliac area have been denuded The lower flap, roughly shaped like an inverted V, is reflected downward and need not necessarily be thin as it is part of the surgical specimen Dissection is started from above downward, removing fascia, fat, and lymphatic tissue en bloc The inguinal canal and femoral vessels are exposed and cleared This bulk of tissue is reflected downward and left attached to the specimen The first stage of the groin dissection has now been completed

The edge of the inguinal ligament is split in its middle The cut ends of the

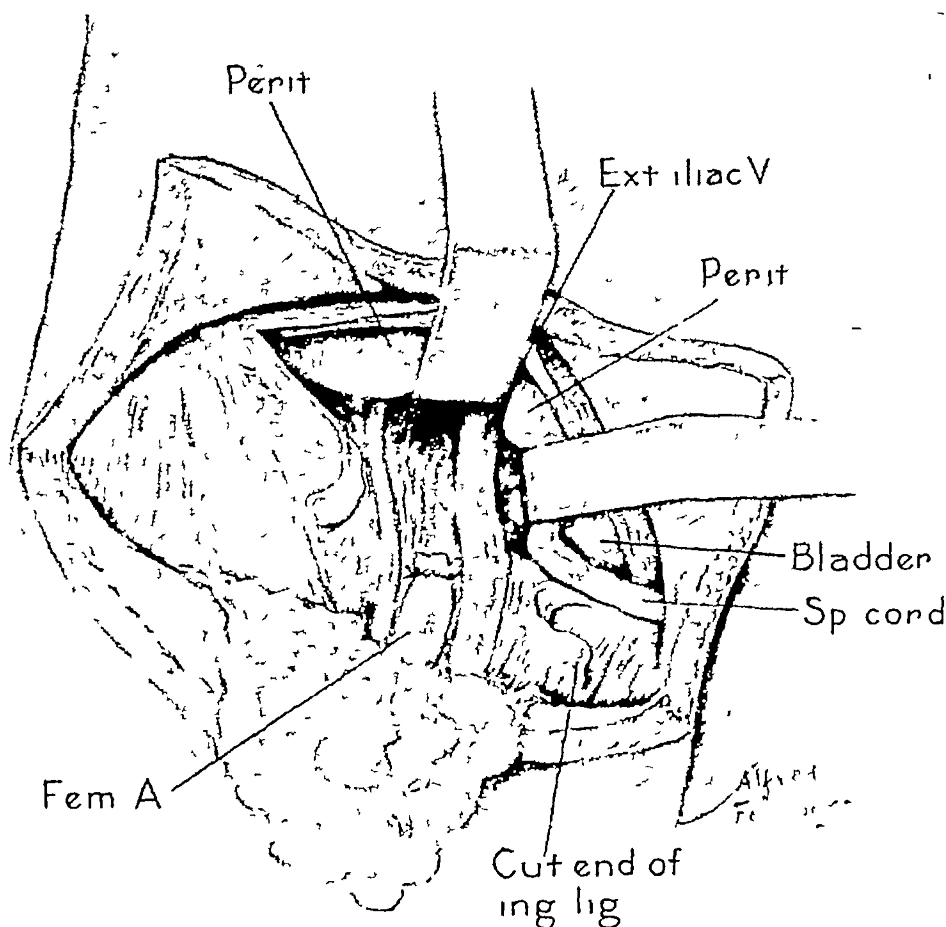


FIG 43 The inguinal ligament has been severed Peritoneum and bladder are retracted upward and medially, exposing the retroperitoneal space and its contents (In this illustration the deep epigastric vessels have been ligated and divided) Lymph nodes and fatty areolor tissue accompanying the external iliac vessels are dissected from above downward The femoral artery is ligated and divided above its profunda branch This completes the deep iliac dissection (second stage of radical groin dissection) and hip-joint amputation may now be proceeded with in the usual manner (Pack and Ehrlich, Ann Surg *123* 965, 1946 *Courtesy*, J B Lippincott Company)

ligament are retracted, and the retroperitoneal space is entered. The deep epigastric artery is frequently not preserved. The peritoneum and abdominal viscera are retracted upward and medially using deep retractors (Care must be taken at this point not to open the peritoneum or to injure the urinary bladder) This maneuver exposes the iliac vessels and retroperitoneal lymphatic tissues If necessary the external oblique and transversalis muscles and fascia can be incised vertically upward, exposing the retroperitoneal space and its contents well beyond the bifurcation of the aorta The chain of lymph nodes fat, and areolar tissue along the external iliac vessels are dissected from above downward, including those overlying the obturator foramen and removed en bloc. On completion of this deep iliac or second stage of groin dissection the common femoral artery is doubly ligated and divided above the profunda femoris the outlined incisions are deepened through subcutaneous tissue and fascia in their entirety and the operation of hip-joint disarticulation is completed in the usual manner

The wound closure will vary with the amount of skin which has been removed In most cases the suture line of the approximated skin flaps will be situated on the lateral aspect of the pelvis and stump and will turn medially along the stump toward the perineum A stab wound is made in the large medial flap which overlies the lower half of the anterior abdominal wall, through which the wound is drained A drain is also allowed to emerge through the most dependent portion of the sutured incision Because of the extensive thin flaps which have been developed it is essential that a bulky pressure dressing be applied These skin flaps like skin grafts must be maintained snugly and uniformly against the underlying tissue bed. The pressure dressing should be firm enough to prevent pocketing of serum but not

TABLE 10 FIVE YEAR END RESULTS FOLLOWING HIP JOINT DISARTICULATION IN RELATION TO METASTASIS FOUND AT OPERATION

End Result	*All Cases*			*Tumors of Skin*			*Tumors of Soft Somatic Tissues*			*Tumors of Bone*		
	All Cases	*Metastasis Present*	*Metastasis Absent*	*All Cases*	*Metastasis Present*	*Metastasis Absent*	*All Cases*	*Metastasis Present*	*Metastasis Absent*	*All Cases*	*Metastasis Present*	*Metastasis Absent*
Determinate cases	52	24	28	18	15	3	30	7	23	4	2	2
Failures—died with cancer	44	20	24	14	12	2	26	6	20	4	2	2
Successful results	8	4	4	4	3	1	4	1	3	0	0	0
Survived over 5 yr without cancer died of other causes	1	0	1	1	0	1	0	0	0	0	0	0
Living without cancer	7	4	3	3	3	0	4	1	3	0	0	0

TABLE 11 PATIENTS SURVIVING FIVE YEARS WITHOUT CANCER FOLLOWING HIP-JOINT DISARTICULATION

Sex	*Age*	*Previous Treatment*	*Location of Primary Tumor*	*Date of Operation*	*Histologic Type of Tumor*	*End Results*
F	19	4 local excisions (Amputation of first toe)	First toe	1-28-31	Malignant neurilemmoma	Living without evidence of cancer, 24 yr
M	59	2 local excisions	Thigh	5-23-31	Malignant neurilemmoma	Lived over 15 yr without evidence of cancer, then lost to follow-up
M	61	None	Subungual great toe	2-14-46	Melanoma	Lived 5 yr. 2 mo without evidence of cancer Died of other causes
F	55	None	Thigh	6-17-46	Fibrosarcoma	Living without evidence of cancer, 8 yr 9 mo.
F	39	3 local excisions (Midthigh amputation)	Thigh	1-24-47	Myxoliposarcoma	Living without evidence of cancer, 8 yr
M	37	2 local excisions	Leg	7-21-47	Melanoma	Living without evidence of cancer, 7 yr 9 mo
M	32	Amputation and irradiation	Leg	1-23-48	Squamous carcinoma	Living without evidence of cancer, 7 yr
M	38	Excision	Leg	10-18-48	Melanoma	Living without evidence of cancer, 6 yr 5 mo

TABLE 12 FIVE-YEAR END RESULTS FOLLOWING HIP-JOINT DISARTICULATION

End Results	*All Cases*	*Tumors of Skin*	*Tumors of Soft Somatic Tissues*	*Tumors of Bone*
All cases, 1926–1953	94	43	41	10
Indeterminate cases	4	1	2	1
3 patients lost to follow-up				
1 patient died of other causes under 5 yr				
Determinate cases, 1926–1953	90	42	39	9
Determinate cases, 1949–1953	38	24	9	5
Determinate cases, 1926–1948, for evaluating 5-yr -cure rate	52	18	30	4
Failures—*Total*	44	14	26	4
Died as a result of cancer	44	14	26	4
Successful results—*Total*	8	4	4	0
Survived over 5 yr. without cancer, died of other causes	1	1	0	0
Living without cancer	7	3	4	0
End results				
Successful results divided by determinate cases, 1926–1948	8/52 (15 4 per cent)	4/18 (22 3 per cent)	4/30 (13 3 per cent)	None

too firm, otherwise necrosis of the flaps will occur

COMPLICATIONS AND CLINICAL COURSE

The postoperative course, like that following straight amputation through the hip joint, is essentially uneventful except for wound complications The utilization of extensive and very thin skin flaps with an impoverished blood supply sometimes produces a certain amount of skin necrosis along the wound margins resulting in infections The inevitable lymphorrhea and pocketing of serum beneath the flaps also encourage infections and contribute to delayed healing

Meticulous wound care, which should include continuous electric motor suction through a sump drain to release the serous transudate or needle aspiration through the flaps to remove accumulated serum and liquefied fat, together with the use of a judiciously applied pressure dressing is an essential feature in the postsurgical management of these cases. Whenever the skin margins of the wound become devitalized, it is well to wait until the necrosis is fairly complete before proceeding with debridement. As with cases of straight radical groin dissection, patients with appreciable skin defects will require grafting, especially if previous radiation therapy has been given to the area By administering adequate amounts of antibiotic medications postoperatively and grafting large de-

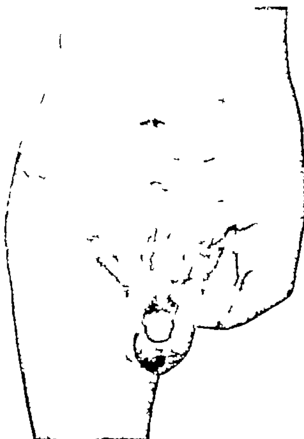


FIG. 44. Postoperative photograph. The absence of an amputation stump following disarticulation of the hip joint makes for prosthetic difficulties. (Pack and Ehrlich, Ann Surg 123 965 1946 *Courtesy* J B Lippincott Company)

fects early the convalescence of patients may be shortened considerably

The problems of prosthesis are similar to those following straight hip-joint disarticulation Apparently the additional procedure of radical groin dissection does not add to the difficulties The shoulder type of artificial limb is also prescribed in these cases

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CHAPTER 12

Sacroiliac Disarticulation (Hemipelvectomy)*

EXCLUSIVE of this series amputation through the sacroiliac joint, not always completed, has been performed 250 times during the past 50 years Seventy five per cent of the operations were performed for neoplastic diseases The infrequency with which this radical amputation has been employed may be ascribed both to the earlier high operative mortality rates and our meager knowledge concerning the clinical behavior of tumors During the past quarter of a century however the operative mortality rate has been gradually lowered from 50 per cent to about 15 per cent. Despite this the procedure is still resorted to with relative infrequency something which cannot be entirely attributed to the mutilating features of the operation.

A surgical procedure especially one of radical variety becomes useful and is increasingly employed only when its indications have been clearly established, the operative mortality rate is low and the end results justify the deformity if there be any The purpose of this section of the present report is to evaluate the usefulness and limitations of sacroiliac disarticulation for malignant tumors and to standardize the surgical technic

* In collaboration with Harry E. Ehrlich.

Definition

The term *sacroiliac disarticulation*, or *exarticulation* of the lower limb through the sacroiliac joint, is used to designate complete removal of a lower extremity

TABLE 13 HEMIPELVECTOMY INCIDENCE ACCORDING TO HISTOLOGIC TYPE OF TUMOR

Histologic Type of Tumor	*Number*	*Per cent age*
Total cases	46	100 0
Tumors of skin—*Total*	11	23 9
Melanoma	8	17 4
Carcinoma	3	6 5
Tumors of soft somatic tissues—*Total*	26	56 5
Liposarcoma	5	10 9
Rhabdomyosarcoma	5	10 9
Malignant neurilemmoma	4	8 7
Fibrosarcoma	3	6 5
Dermatofibrosarcoma protuberans	3	6 5
Synovioma	2	4 3
Kaposi s sarcoma	1	2 2
Extraosseous osteogenic sarcoma	1	2 2
Alveolar soft tissue sarcoma	1	2 2
Sarcoma unclassified	1	2 2
Tumors of bone—*Total*	9	19 6
Chondrosarcoma	6	13 0
Osteogenic sarcoma	2	4 3
Periosteal fibrosarcoma	1	2 2

corresponding buttock, and entire innominate bone in one stage Other names which have been employed for this operation are interpelviabdominal amputation, hemipelvectomy, interilio-sacropubic amputation, transiliac amputation, interinnominoabdominal amputation, hindquarter operation, and disarticulation of the innominate bone

History

The operation was first successfully performed by Girard in 1895 The principles of the surgical procedure were laid down by the English surgeon Hogarth Pringle in 1916 The technic to be described in this report is a modification of the original Pringle operation

In 1916 Pringle reviewed the literature and reported 4 cases of his own The literature was reviewed again by Judin in 1926, Gordon-Taylor in 1935 and 1940, Leighton and Morton in 1942, and more recently by Sugarbaker These authors reported 1, 11, 3, 4, and 6 cases of their own, respectively Approximately one-half of the previously published cases survived the operation Thirty-five per cent of the tumor patients who survived the operation were reported to be clinically cured

Table 14 Sex and Age of Patients Who Underwent Hemipelvectomy

Type of Tumor	*Total*	*Male*	*Female*	*Youngest Patient*	*Oldest Patient*
Total	46	26	20	15, female	61, male
Tumors of skin	11	6	5	21, male (melanoma)	53, male (melanoma)
Tumors of soft somatic tissues	26	14	12	15, female (mal neurilemmoma)	61, male (dermatofibrosarcoma)
Tumors of bone	9	6	3	34, male (chondrosarcoma)	60, male (chondrosarcoma)

Table 15 Five-year End Results Following Hemipelvectomy

End Results	*All Cases*	*Tumors of Skin*	*Tumors of Soft Somatic Tissues*	*Tumors of Bone*
All cases 1944–1953	46	11	26	9
Indeterminate cases—*Total*	5	0	3	2
Lost to follow-up	3	0	2	1
Died of other causes	2	0	1	1
Determinate cases, 1944–1953	41	11	23	7
Determinate cases, 1949–1953	27	11	13	3
Determinate cases, 1944–1948, for evaluating 5-yr -cure rate	14	0	10	4
Failures—*Total*	11	0	9	2
Died as result of cancer	10	0	8	2
Living with cancer	1	0	1	0
Successful results—*Total*	3	0	1	2
Living without cancer over 5 yr				
End results				
Successful results divided by determinate cases, 1944–1948	3/4 (21 4 per cent)	None	1/10 (10 per cent)	2/1 (50 per cent)

INDICATIONS

Sacroiliac disarticulation is indicated for primary malignant osseous and periosteal tumors of the upper femur when the growth has extended to or through the hip joint and for similar neoplasms of the innominate bone. Primary bulky malignant tumors of the soft somatic tissues of the upper thigh (involving the hip joint or extending through the obturator foramen) groin buttock, pelvic parietes, and iliac region are best treated by amputation through the sacroiliac joint.

This radical amputation occasionally has a definite place in the palliative therapy of cancer Even in the presence of hopeless extension or distant metastasis, fungating ulcerated tumors of the soft somatic tissues of the upper thigh, groin, and buttock may be removed in selected cases by sacroiliac disarticulation and gratifying results may thus be obtained, provided the patient s general condition has not deteriorated too much Elimination of sepsis and pain and conversion of a foul-smelling, bedridden patient to comfort and partial activity can be accomplished in certain hopelessly advanced cases When the entire lower limb and groin are the seat of an uncontrolled infected neoplastic process like Kaposi's disease, palliation may be provided by amputation through the sacroiliac joint.

Massive osteochondromas of the innominate bone and massive plexiform neurofibromas involving the upper thigh, groin, and hip joint or the buttock and pelvic parietes are best treated by exarticulation of the lower limb through the sacroiliac joint, if the tumors contain histologically atypical areas and if they cannot be adequately removed by wide local excision or some other type of conservative operation.

Possible involvement of the pelvic and abdominal viscera should always be investigated by careful physical, roentgenographic, and endoscopic examinations If necessary preliminary celiotomy should be performed to ascertain the extent of the growth and possible peritoneal involvement. Wide extension of the neoplasm should not always deter the surgeon from performing the operation.

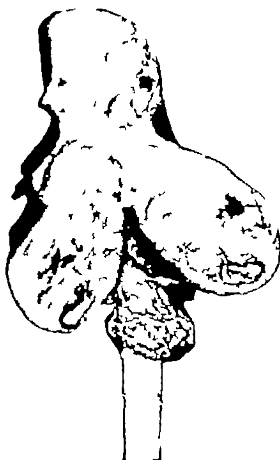


FIG. 45 Surgical specimen from amputation through the sacroiliac joint (hemipelvectomy) Massive myxoliposarcoma (specimen bisected) involving the upper thigh and groin and extending over the anterior superior iliac spine Dissection of the hind quarter revealed the tumor to be centered in the iliopsoas muscle Bulky malignant infiltrating tumors of the pelvic *parietes are occasionally* amenable to surgical extirpation by disarticulation of the innominate bone. Patient living and well for 10 years. (Pack, Ehrlich, and Gentil, Surg Gynec. & Obst. *84* 1105 1947 *Courtesy* Surgery Gynecology and Obstetrics.)

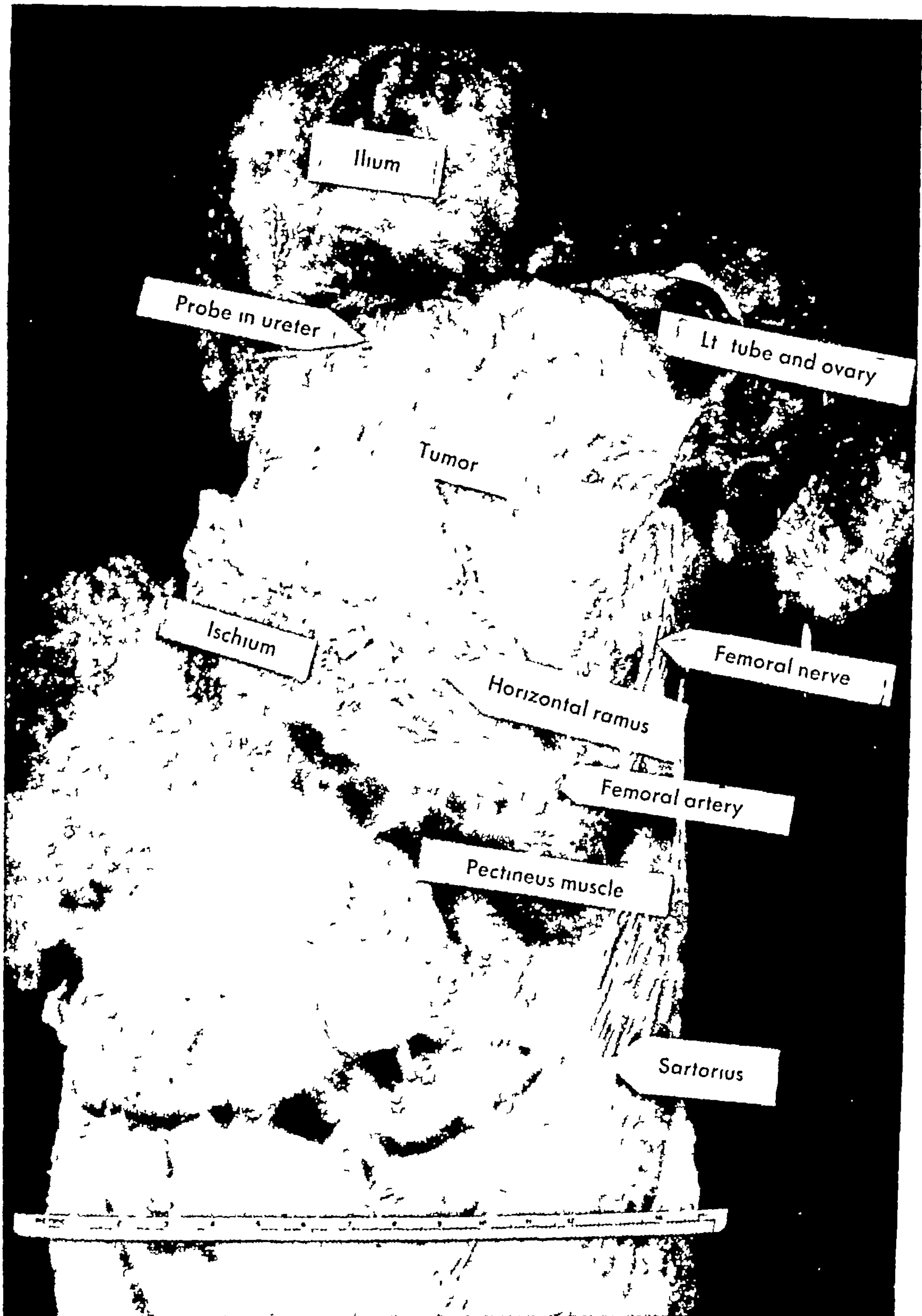


FIG 46 Surgical specimen Massive rhabdomyosarcoma which had resisted attempts at local extirpation Hemipelvectomy, left salpingo-oophorectomy, with resection of the lower end of the left ureter and the establishment of ureterocutaneous anastomosis, were performed in an attempt to control this highly malignant neoplasm. The patient enjoyed palliation but succumbed 18 months later

PREOPERATIVE CONSIDERATIONS

The preoperative considerations and precautions which were discussed for hip-joint disarticulation are also applicable for cases of sacroiliac disarticulation Douches and surgical cleansing of the vagina, daily antiseptic sprays and dressings, debridement for ulcerated, infected, and necrotic tumors, blood transfusions

for anemic and toxic patients eradication of urinary tract infections and adequate correction of hypoproteinemia and other metabolic factors if present, are essential features in preparing the patient for this radical operation. If the neoplasm is fungating extensively much of the fungating portion may be excised with the cautery several days before amputation is performed. In this way the operative field can be more thoroughly prepared. The application of an elastic bandage to the affected limb (except in cases of melanoma) and preoperative cleansing of the bowel with colonic irrigations are highly desirable. A Foley urethral catheter is inserted into the bladder before the patient is taken into the operating room

OPERATIVE TECHNIC

After the operative area has been cleansed and prepared, the anal opening is closed with a purse-string suture, and, in the male, the scrotum is sutured to

TABLE 16 TYPE OF TUMOR AND END RESULTS FOLLOWING HEMIPELVECTOMY

		Patients Who Have Died			*Patients Who Are Living*				
							Without Cancer		
Type of Malignant Tumor	*Total Cases*	*Total Cases*	*With Cancer*	*Without Cancer*	*Total Cases*	*With Cancer*	*Under 5 Yr*	*5–10 Yr*	*Over 10 Yr*
Total cases	46*	28†	26	0	15	2	10	3	0
Tumors of skin—*Total*	11	8	8	0	3	1	2	0	0
Melanoma	8	6	6	0	2	1	1	0	0
Carcinoma	3	2	2	0	1	0	1	0	0
Tumors of soft somatic tissues—*Total*	26‡	15§	14	0	9	1	7	1	0
Liposarcoma	5‖	2	2	0	2	0	1	1	0
Rhabdomyosarcoma	5	3	3	0	2	0	2	0	0
Malignant neurilemmoma	4‖	3	3	0	0	0	0	0	0
Fibrosarcoma	3	1	1	0	2	1	1	0	0
Dermatofibrosarcoma protuberans	3	2	2	0	1	0	1	0	0
Synovioma	2	1	1	0	1	0	0	0	0
Kaposi s sarcoma	1	1	1	0	0	0	0	0	0
Extraosseous osteogenic sarcoma	1	1§	0	0	0	0	0	0	0
Alveolar soft part sarcoma	1	0	0	0	1	0	1	0	0
Sarcoma unclassified	1	1	1	0	0	0	0	0	0
Tumors of bone—*Total*	9‖	5§	4	0	3	0	1	2	0
Chondrosarcoma	6‖	2	2	0	3	0	1	2	0
Osteogenic sarcoma	2	2	2	0	0	0	0	0	0
Periosteal fibrosarcoma	1	1§	0	0	0	0	0	0	0

* Three cases lost to follow-up
† In two cases death due to other causes
‡ Two cases lost to follow up
§ In one case death due to other causes
‖ One case lost to follow up

the opposite thigh The skin of the entire field is again painted, and the patient is draped

An incision is made from a point just above the pubic tubercle and extending upward and outward to a point just beyond the iliac crest This incision corresponds to the curve of the inguinal ligament and the iliac crest The posterior flap is outlined by carrying the lateral termination of the anterior incision downward, coursing above the greater trochanter and along the infragluteal groove to the perineum It is then joined with the medial end of the anterior incision at the superior border of the symphysis pubis

The anterior incision is deepened through subcutaneous tissues and fascia in its entirety The rectus abdominis is divided at its insertion into the pubic bone The inguinal ligament is severed at its lateral attachment to the pubis In this way the anterior abdominal wall is actually detached from the bony pelvis, forming the anterior flap The spermatic cord is preserved and retracted.

The peritoneum is stripped off, and the abdominal contents are pushed upward and medially, the urinary bladder is pushed downward and medially The iliac fossa and its contents are thus exposed Three structures—peritoneum, intestines, and bladder—must be constantly retracted during the anterior dissection The ureter must also be identified The external iliac artery is doubly ligated and divided. The external iliac vein is not ligated at this time in order to allow for a maximum return of blood

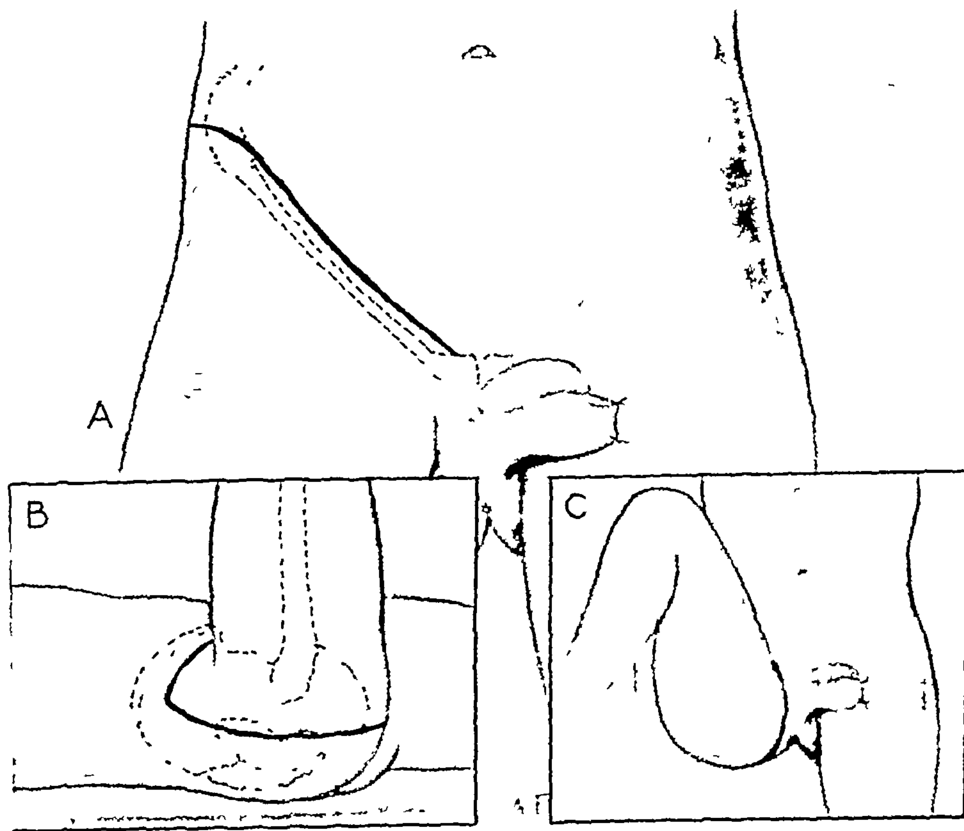


Fig 47 Incision for sacroiliac disarticulation A The anterior incision extends from the pubic tubercle to beyond the iliac crest, paralleling the inguinal ligament B The posterior flap is outlined by carrying the lateral termination of the anterior incision downward, coursing above the greater trochanter and along the infragluteal fold to the perineum C The anterior and posterior incisions are then joined at the superior border of the symphysis pubis (Pack and Ehrlich, Ann Surg *121* 1, 1946 *Courtesy*, J B Lippincott Company)

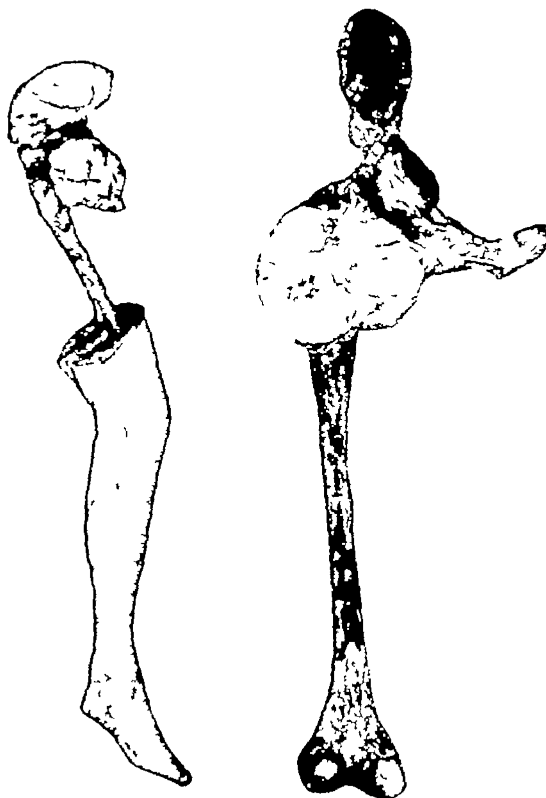


FIG. 48. (*Left*) Operative specimen of a bulky fibrosarcoma which invaded the ischium, hip joint and greater trochanter necessitating sacroiliac disarticulation. (*Right*) Close-up of left figure showing invasion of hip joint and pelvic bone by diffuse fibrosarcoma. A malignant tumor so located can only be completely removed by sacroiliac disarticulation. (Pack and Ehrlich, Ann. Surg *124* 1 1946 *Courtesy* J B Lippincott Company)

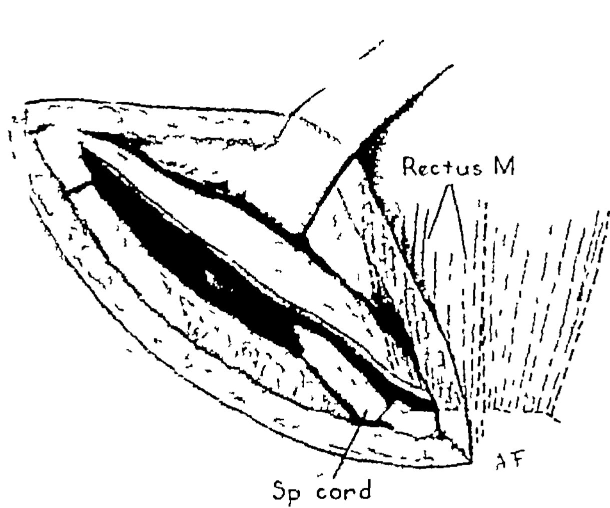


Fig 49 Sacroiliac disarticulation The pubic insertion of the rectus abdominis muscle has been cut The medial and lateral attachments of the inguinal ligament have been severed Thus, the anterior abdominal wall is detached from the bony pelvis The spermatic cord is preserved (Pack and Ehrlich, Ann Surg *124* 1, 1946 *Courtesy,* J B Lippincott Company)

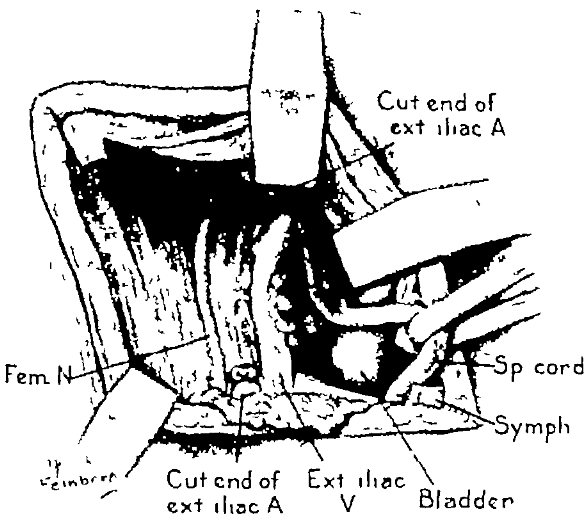


Fig 50 The retroperitoneal space has been exposed by pushing the peritoneum, its contents, and the urinary bladder upward and medially The external iliac artery has been ligated and divided The external iliac vein is ligated later (Pack and Ehrlich, Ann Surg *124* 1, 1946 *Courtesy,* J B Lippincott Company)

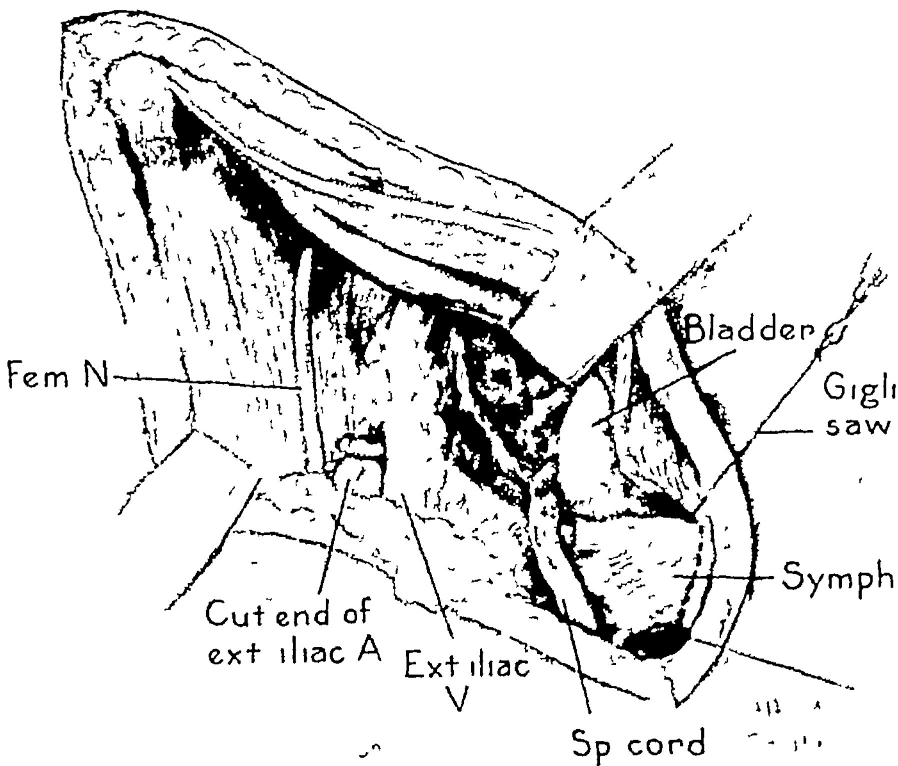


Fig 51 The symphysis pubis is skeletonized and then divided with a Gigli saw The bladder must be retracted well out of the way during this phase of the operation The symphysis must be clearly identified, otherwise the corresponding or contralateral pubic arch will, instead, be transected (Pack and Ehrlich, Ann Surg *124* 1, 1946 *Courtesy,* J B Lippincott Company)

from the limb The pubic symphysis is exposed, skeletonized, and easily divided with a Gigli saw or chisel.

The symphysis must be clearly identified, otherwise the corresponding or contralateral pubic arch will instead be transected Considerable bleeding not infrequently follows separation of the symphysis pubis due to cutting of vascular erectile tissue (ischiocavernosus) Hemorrhage is promptly controlled by packing The posterior skin flap is developed as far back as the sacrum.

The anterior dissection is continued The crest of the ilium is skeletonized, including severance of the attachment of the quadratus lumborum muscle The

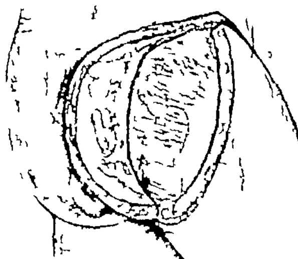


FIG. 52. The posterior skin flap is developed as far back as the sacrum. (Pack and Ehrlich Ann. Surg 124 1 1946 Courtesy J B Lippincott Company)

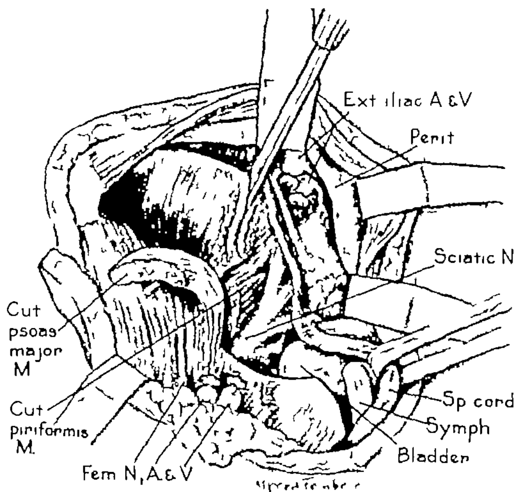


FIG. 53 Anterior dissection continued. The ilium has been completely skeletonized, and the external iliac vein has finally been ligated and divided. The sacroiliac joint is exposed by transecting and reflecting all the overlying muscles. Disarticulation of this joint is best performed during the anterior dissection phase of the operation. Bevel of chisel and direction of the instrument *must be away from the midline* (Pack and Ehrlich, Ann Surg 124 1 1946 *Courtesy* J B Lippincott Company)

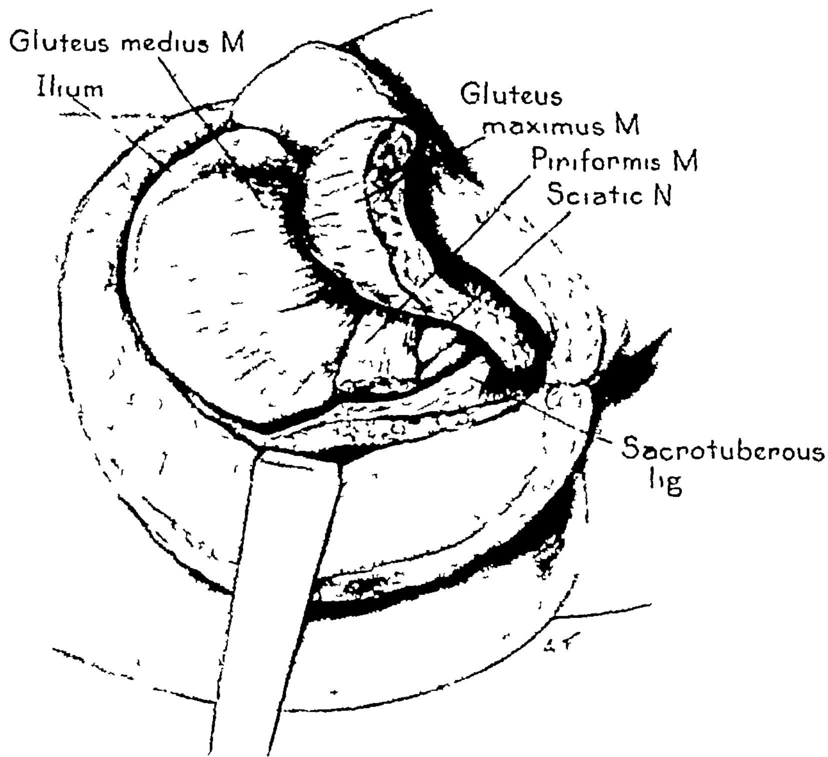


Fig 54 Posterior dissection After partition of the sacroiliac joint, the patient is turned on the unaffected side, and the innominate bone is further mobilized by transecting the sacral musclar attachments The specimen is now attached to the patient only by the major ligaments of the sacrum and the great nerve trunks of the lumbar and sacral plexuses (Pack and Ehrlich, Ann Surg *124* 1, 1946 *Courtesy* J B Lippincott Company)

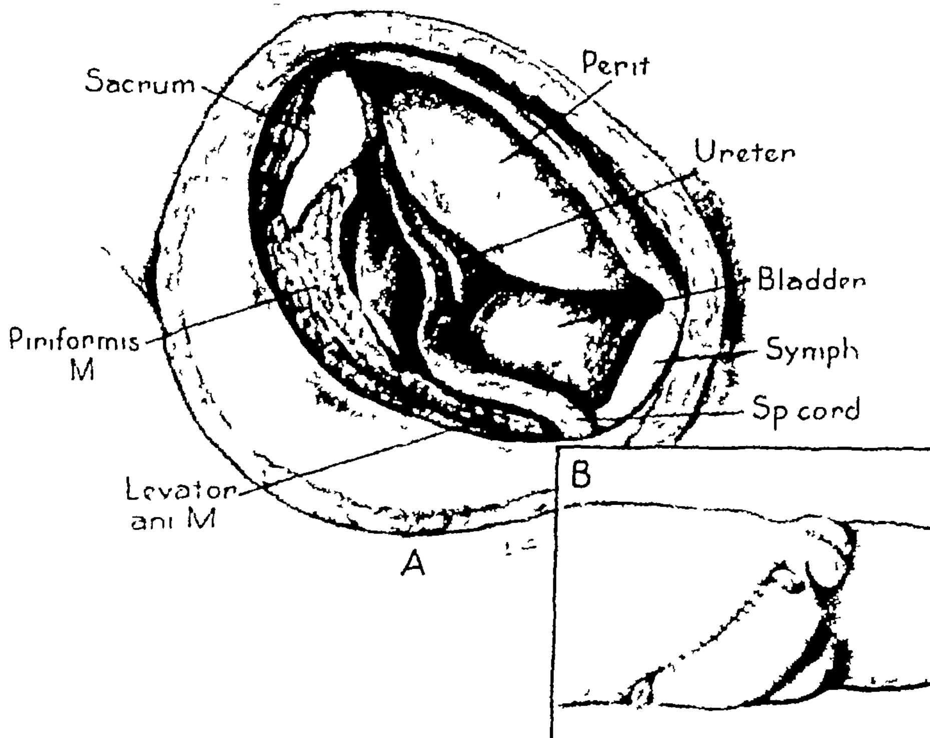


Fig 55 A Amputation through sacroiliac joint completed *B* Wound closure (Pack and Ehrlich, Ann Surg *124* 1, 1946 *Courtesy*, J B Lippincott Company)

external iliac vein is now doubly ligated and divided, but the internal iliac vein is preserved. The iliopsoas muscle is then transected as high as possible The iliacus piriformis, gamelli, and levator ani muscles are divided, and the sacro-iliac joint is exposed

Disarticulation of this joint is per formed during the anterior phase of the dissection by using a chisel. Leverage downward on the lateral aspect of the ilium will dislocate the joint, making its severance more easily accomplished. The bevel of the chisel and the direction of the instrument must be away from the midline. Injury to the hypogastric vein must especially be avoided at this time. The sacroiliac synchondrosis is divided with relative ease If difficulty is encountered, it is most probable that the ilium down through the sacrosciatic notch is being cut through rather than the synchondrosis Troublesome bleed ing which occasionally follows division of the sacroiliac joint is controlled by packing and pressure.

The patient is turned on the unaf fected side, and the posterior dissection is carried out. The posterior attachments of the gluteal muscles are divided The limb is then sharply flexed and adducted. The specimen is now attached to the patient only by the major ligaments of the sacrum and the great nerve trunks The ligaments are divided from below upward, and the gluteal and obturator arteries are caught, cut, and ligated. The specimen is removed.

The large nerve trunks of the lumbar and sacral plexuses are injected with al cohol and ligated. Absolute hemostasis is obtained Redundant skin and muscle tags are trimmed, and the wound is thor oughly irrigated with saline solution The posterior flap is usually much longer than the anterior This inequality is cor rected by a *V plasty* removing a central V-shaped section and then by approxi mation leaving a T-shaped wound The flaps are approximated with interrupted stitches after two cigarette drains have been placed in the defect and allowed to emerge through the ends of the wound The temporary scrotal and anal sutures are removed, and a bulky pressure dress ing is applied.

Anterior Dissection

With this technic all of the major phases of the operation are performed through an anterior approach except for division of the sacral ligaments, lumbar nerve trunks and gluteal and obturator arteries The contents of the iliac fossa are easily exposed, and the peritoneum intestines, and bladder can be retracted well out of the way protecting them from possible injury Both synchondroses may also be adequately exposed, cleared, and divided under direct vision with little difficulty by approaching them an-teriorly Furthermore it will not be necessary to turn the patient, occasion ally in shock, too often in order to ex pose the necessary anatomic structures. The patient is turned only on three occasions once for outlining the pos terior incision, again for development of the posterior flap and a third time when the posterior dissection or final phase of the amputation is performed.

Ligation of the Common Iliac Artery

Amputation through the sacroiliac joint may be performed in a relatively bloodless manner if the common, rather than the external, iliac artery is ligated In this way there is no vigorous bleed ing when the parietal branches of the hypogastric artery are cut, and the amount of bleeding which follows di vision of the pubic and sacroiliac syn chondroses is amazingly small. Ligation of the common iliac artery however has some drawbacks and should not be done routinely When it is ligated a central

V-shaped ischemic segment of the posterior flap is excised

Ligation of the common iliac artery may be indicated in poor-risk patients for whom excessive bleeding, shock, and a prolonged operation are to be avoided at all costs Under such circumstances it is preferable to risk possible necrosis of the posterior flap with its sequelae rather than an operative death A wide and deep V-shaped excision of a large wedge of the lower and longer margin of the wound usually prevents necrosis This procedure leaves a T-shaped scar

CRITICAL PERIOD OF THE OPERATION

The critical period of the operation is during partition of the sacroiliac synchondrosis at which time shock occasionally occurs Since the posterior dissection with subsequent division of the gluteal and obturator arteries immediately follows as the next step in the operation, it is essential that the blood pressure be

TABLE 17 PREVIOUS TREATMENT IN RELATION TO END RESULTS AFTER HEMIPELVECTOMY 1944–1953

Type of Previous Treatment	*All Cases*			*Tumors of Skin*			*Tumors of Soft Somatic Tissues*			*Tumors of Bone*		
	Total	*Died*	*Living*	*Total*	*Died*	*Living*	*Total*	*Died*	*Living*	*Total*	*Died*	*Living*
All cases	46*	28	15	11	8	3	26†	15	9	9‡	5	3
No previous treatment	12	7	5	1	1	0	6	3	3	5	3	2
Excision only	18†	10	6	3	2	1	13‡	7	5	2‡	1	0
Excision & irradiation	3	3	0	0	0	0	2	2	0	1	1	0
Excision & dissection	4	2	2	3	1	2	1	1	0	0	0	0
Excision, dissection, & amputation	1	1	0	0	0	0	1	1	0	0	0	0
Excision, dissection, & irradiation	1‡	0	0	0	0	0	1‡	0	0	0	0	0
Excision & amputation	1	0	1	0	0	0	1	0	1	0	0	0
Excision, amputation, & irradiation	2	1	1	1	1	0	0	0	0	1	0	1
Irradiation only	1	1	0	0	0	0	1	1	0	0	0	0
Dissection & amputation	1	1	0	1	1	0	0	0	0	0	0	0
Amputation only	1	1	0	1	1	0	0	0	0	0	0	0
Amputation, dissection & irradiation	1	1	0	1	1	0	0	0	0	0	0	0

* Three cases lost to follow-up
† Two cases lost to follow-up
‡ One case lost to follow-up

maintained within reasonably normal limits before the posterior dissection is begun, because it is during this last phase of the procedure that further appreciable hemorrhage might be encountered. Accordingly we routinely start a second blood transfusion in the contralateral foot as a precautionary measure just prior to disarticulation of the sacroiliac joint, so that the patient is not in shock at the time the specimen is removed.

Skin Grafting

In the event that a considerable portion of the anterior or posterior abdominal walls must be included in the amputation because of involvement by tumor or radiation injury the skin flaps might not be adequate for primary wound closure Under such circumstances sufficient skin may be readily removed from the amputated specimen with the dermatome to cover the defect.

POSTOPERATIVE COMPLICATIONS

Aside from the distressing pains of phantom limb a satisfactory postoperative course may be expected provided the proper prophylactic measures to prevent complications specific for cases of sacroiliac disarticulation are instituted.

Abdominal Distention

This is practically a constant and occasionally disturbing postsurgical complication The etiology is obscure Retraction and manipulation of the peritoneal contents for approximately 2 hours during the operation probably are not responsible for this complication Division of the large nerve trunks of the lumbar and sacral plexuses might conceivably depress the celiac and superior and inferior mesenteric sympathetic plexuses and thus account for the ileus If a Levine tube is placed in the stomach as soon as the patient has fully reacted from the anesthesia and constant Wangensteen suction is continued for from 48 to 72 hours serious abdominal distention can be avoided. During this period fluid and electrolyte imbalance must be corrected and hypoproteinemia, a not uncommon complication combated by administration of large amounts of plasma

Paresis of the Urinary Bladder

Inability to void, due to paresis of the bladder occurs often but is only temporary lasting four to seven days A Foley urethral catheter should be placed in the bladder before the patient is taken into the operating room. Thus the bladder is kept empty during the operation and is less likely to be injured. When the patient is returned to his bed, urinary tidal drainage is established and maintained for about one week. Not only is this method of catheter drainage beneficial to the atonic bladder but it also prevents soiling of the dressing during the first postoperative week When the catheter is finally removed, the patient voids spontaneously No instance of postsurgical urinary tract infection was encountered.

Wound Healing

Continued and often profuse drainage for a period of about two weeks is almost a constant feature following sacroiliac disarticulation This may be attributed to necrosis of muscle tags, lymphorrhea, and liquefaction of fat Necrosis of skin flaps will occur if the blood supply is inadequate or if the tissues have been devitalized by roentgenotherapy If the tumor has been previously heavily irradiated, every effort should be made to excise all of the irradiated skin, otherwise delayed healing or nonhealing is inevitable

Frank wound infections were commonly encountered despite exhaustive

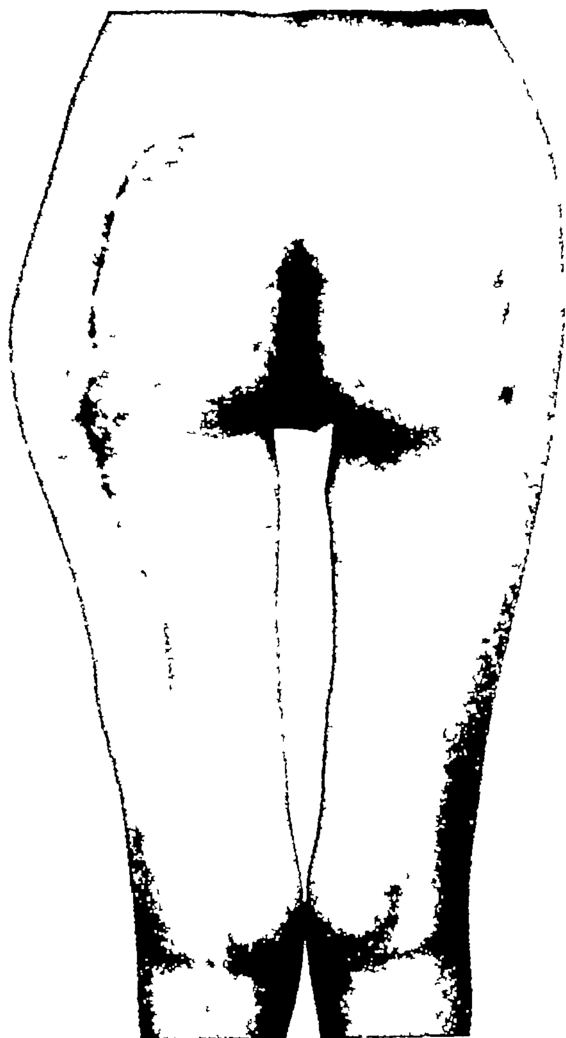


Fig 56 Malignant neurilemmoma developing in sciatic nerve and extending through obturator foramen to involve pelvic parietes This extension was first determined by exploratory operation through the thigh and buttock (Pack and Ehrlich, Ann Surg *124* 1, 1946 *Courtesy,* J B Lippincott Company)

preoperative prophylactic measures, which are discussed elsewhere in this report, and adequate postoperative chemotherapy. The proximity of the operative area to the anus and genitals, the ulcerated, necrotic, and extensively infected state of many of the neoplasms, and postoperative anemia and hypoproteinemia, together with a frequent history of heavy irradiation to the tumor, were the factors which contributed to the high incidence of postsurgical wound infections There were no instances of vesical, enteric, or ureteral fistula, or permanent sinus formation in our cases or in any of the previously reported cases in which the operation was performed for neoplastic disease

Osteomyelitis was encountered in one instance At this operation the contralateral pubic arch was divided, instead of the pubic symphysis, thus exposing cancellous bone. Since the tumor had been extensively infected and previously heavily irradiated, this complication was inevitable.

Anemia

This is a characteristic postoperative manifestation following sacroiliac disar-

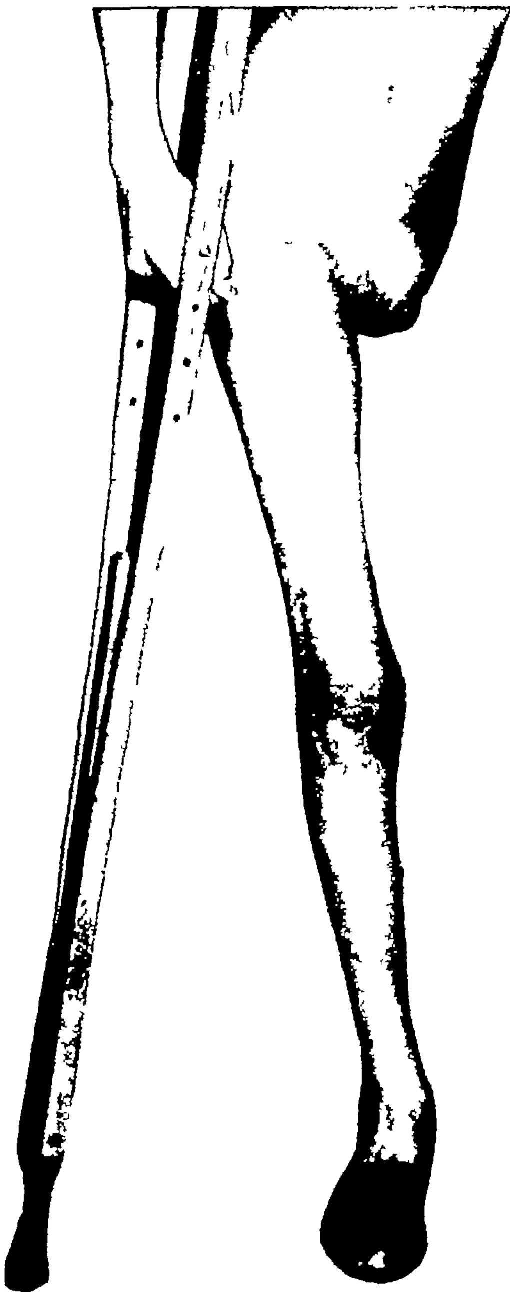


Fig 57 Postoperative photograph showing deformity, same patient as Figure 56 (Pack and Ehrlich, Ann Surg *124* 1, 1946 *Courtesy,* J B Lippincott Company)

ticulation but does not consistently appear after hip-joint, interscapulothoracic, or any other type of amputation. Naturally patients who require sacroiliac disarticulation are not infrequently anemic because of sepsis, radiation therapy or malnutrition due to pain. In these cases the blood picture is brought to within reasonably normal limits by appropriate



Fig. 58. Subsequent pelvic roentgenogram of patient in Figs 56 and 57 showing fetal skeleton.



Fig. 59 Interilioabdominal amputation (hemipelvectomy) Utilization of large anterior flap to cover defect caused by sacrifice of large posterior pelvic segment including buttock. (*Courtesy* L. Bowden and R. J Booher and Cancer *6* 69 1953.)



Fig. 60 Massive chondrosarcoma of bony pelvis which has extensively infiltrated the soft somatic tissues interilioabdominal amputation (hemipelvectomy) Almost complete replacement of pubes and ischium by tumor



Fig. 61 Postoperative roentgenogram showing absence of resected half of the pelvis following the performance. (Pack and Ehrlich, Ann. Surg. *124* 1 1946 *Courtesy* J B Lippincott Company)

preoperative measures Some of the patients may lose considerable blood during the operation. This loss however is adequately replaced by blood transfusions In those cases in which the blood loss is 500 cc. or less anemia still appears

during the immediate postsurgical period It also occurs when massive blood transfusions are not given during the operation and, therefore, cannot be attributed to excessive destruction of red cells in the spleen with subsequent bone marrow depression The anemia can neither be ascribed to blood loss during postoperative days and persists for about three weeks It does not respond to blood transfusion or to liver or iron therapy An increase of reticulocytes in the peripheral blood and of nucleated red cells in the sternal marrow was also noted postoperatively, an indication of compensatory marrow hyperplasia.

TABLE 18 FIVE-YEAR END RESULTS FOLLOWING HEMIPELVECTOMY IN RELATION TO METASTASIS FOUND AT OPERATION

End Results	*All Cases*			*Tumors of Soft Somatic Tissues*			*Tumors of Bone*		
		Metastasis			*Metastasis*			*Metastasis*	
	All Cases	*Present*	*Absent*	*All Cases*	*Present*	*Absent*	*All Cases*	*Present*	*Absent*
Determinate cases, 1944–1948	14	5	9	10	5	5	4	0	4
Failures—*Total*	11	5	6	9	5	4	2	0	2
Died as a result of cancer	10	5	5	8	5	3	2	0	2
Living with cancer	1	0	1	1	0	1	0	0	0
Successful results									
Living without cancer	3	0	3	1	0	1	2	0	2

TABLE 19 PATIENTS SURVIVING FIVE YEARS WITHOUT CANCER FOLLOWING HEMIPELVECTOMY

Sex	*Age*	*Previous Treatment*	*Location of Primary Tumor*	*Date of Operation*	*Histologic Type of Tumor*	*Postoperative Duration*
M	60	None	Right ischium and pubis	1-9-45	Chondrosarcoma	9 yr
M	40	Excision	Thigh and groin	1-14-45	Myxoliposarcoma	8 yr
M	45	3 Excisions, amputation & irradiation	Femur	3-4-47	Chondrosarcoma	5 yr 8 mo

operation nor to any specific systemic preoperative factors It is not unlikely, therefore, that *removal of an entire* lower extremity and innominate bone deprives the hemopoietic system of sufficient active bone marrow to produce anemia This normocytic, normochromic anemia is noted during the first few

FUNCTION OF ANAL SPHINCTER

Fecal incontinence or other disturbances of sphincteric control do not occur following sacroiliac disarticulation despite complete division of the levator ani muscles on the affected side This may be attributed to the cross-insertion of

these muscles so that the preserved sphincter and intact contralateral levator ani muscles are wholly adequate for satisfactory sphincteric control.

HERNIA

The abdominal contents are merely supported by skin, subcutaneous tissue fasciae and peritoneum yet there has been no instance of herniation. There is no need, therefore, for preserving the gluteus maximus muscle since it does not materially make for a better stump No device for supporting the abdominal wall is necessary although one has been introduced.

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CHAPTER 13

Interscapulothoracic Amputation for Malignant Tumors of the Upper Extremity*

INTERSCAPULOTHORACIC amputation is an operation devised to remove the entire upper extremity the shoulder girdle, and its muscular attachments The operation has been variously designated as "removal of one-half of the shoulder girdle" by von Eiselsberg, "surgical removal of the breast girdle" by Adelmann, and "extirpation of the arm and shoulder" by Kocher but it is the term *interscapulothoracic amputation* which the French surgeons notably Berger have employed and which now enjoys popular usage.

In *Anatomy of the Human Body* by W Cheselden there is a note and illustration concerning the case of Samuel Wood, a miller who in 1737 survived a traumatic amputation of an arm and shoulder by the cogs of a mill wheel Only slight shock was said to have followed this amputation by avulsion The English surgeon R. Cumming has been generally accredited with having performed the first elective operation of this type, which was for a gunshot wound, although Halstead maintained that Larrey was the originator of the formal procedure as it is done today Dixie Crosby in 1836, was the first American surgeon to perform a successful extirpation of the shoulder girdle for tumor In 1837 Musey of Cincinnati did a scapulectomy following a disarticulation of the humerus for sarcoma the patient survived 30 years

Until 1881 *i e* before the era of antisepsis there were recorded interscapulothoracic amputations for various indications with an operative mortality of 38 0 per cent. The technic of the operation was standardized by Berger and the classic procedure still bears his name. In 1887 he described all the previously published cases and added his own experience with the operation, for which his mortality rate was 10 4 per cent. A most important article on this subject was written by Buchanan of Pittsburgh who analyzed all the cases reported prior to the year 1900 At that time the opera

* In collaboration with Fernando Gentil

tion was so unusual as to be a surgical curiosity, and surgeons were inclined to rush their individual case reports into print before final end results could be appreciated Buchanan, by letter and consultation, secured most of the follow-up data on 14 interscapulothoracic amputations which were done prior to the year 1900

INDICATIONS FOR INTERSCAPULOTHORACIC AMPUTATION

The necessity for performing such a massive, disabling, and disfiguring amputation demands a clear conception of the indications, hazards, natural history of the tumor responsible, and possible end results to be achieved The idea of sacrificing the clavicle, scapula, and arm with their muscular attachments is so repugnant to most patients and repellent to many surgeons that one of three sequences is apt to follow. The patient refuses with finality all operative aid, accepts a more conservative though less certain treatment, or eventually agrees after a prolonged interval during which the cancer advances to the stage in which an operation of desperation is substituted for what was originally an operation of hope It may be said in all fairness to the operation, which is unquestionably well conceived, that too few of them are done as carefully planned, elective, initial procedures and that too many are performed as a last resort, following one or more recurrences after incomplete or more conservative operations The indetermination or reluctance of the patient is not a contraindication from the surgeon's viewpoint The ultimate psychologic effect of this operation on our patients has not been bad, those who are living are apparently happily adjusted to this handicap

TABLE 20 INTERSCAPULOTHORACIC AMPUTATION INCIDENCE ACCORDING TO HISTOLOGIC TYPE OF TUMOR

Histologic Type of Tumor	*Number*	*Percentage*
Total cases	88	100 0
Tumors of skin, primary in extremity—*Total*	27	30 7
Melanoma	21	23 9
Carcinoma	6	6 8
Tumors of skin, primary elsewhere—*Total*	6	6 8
Melanoma	1	1 1
Carcinoma	5	5 7
Tumors of soft somatic tissues—*Total*	47	53 4
Rhabdomyosarcoma	14	15 9
Fibrosarcoma	8	9 1
Synovioma	7	8 0
Sarcoma unclassified	6	6 8
Malignant neurilemmoma	5	5 7
Angiosarcoma	4	4 5
Reticulum-cell sarcoma	1	1 1
Liposarcoma	1	1 1
Extraabdominal desmoid tumor	1	1 1
Tumors of bone—*Total*	8	9 1
Osteogenic sarcoma	3	3 4
Chondrosarcoma	2	2 3
Endothelial myeloma	1	1 1
Neuroblastoma	1	1 1
Reticulum-cell sarcoma	1	1 1

The indications for this operation are enumerated in the following decalogue.

1 Nonneoplastic conditions, such as extensive trauma with irreparable damage, gunshot wounds, tuberculosis, and incurable osteomyelitis It is not the purpose of this critique to discuss these indications at length

2 Intractable pain caused by incurable tumors of the shoulder girdle even though metastases to lungs are present The purpose here is palliation only, to get rid of a cumbersome, painful, often suppurating extremity (Pollosson, Jeanbrau) This indication is not so valid now that intolerable pain in the shoul-

der and arm can often be controlled by such neurosurgical measures as cervical chordotomy and posterior rhizotomy

3 All malignant tumors requiring dis articulation of the humerus at the shoul der The more major procedure in our experience does not require the penalty of a higher operative mortality The deformity is greater but suitable pros thetic appliances are available, and any good tailor can reconstruct the shoulder of a coat The shoulder without the arm is practically useless There can be no argument about the greater freedom from local recurrence which interscap-ulothoracic amputation affords

of the muscles which pass over the tumor Although a good fundamental prin ciple it is perhaps too radical to be all inclusive, because some malignant neurilemmomas and osteosarcomas of low grade malignancy may be treated more conservatively

6 All malignant tumors invading the shoulder joint capsule

7 Infiltrating malignant tumors in volving the deltoid, subscapularis and pectoral muscles This rule applies in-variably to the unencapsulated malig nant neurilemmomas rhabdomyosar comas, and fibrosarcomas but exceptions are admitted in the case of liposarcomas

TABLE 21 INTERSCAPULOTHORACIC AMPUTATION SEX AND AGE OF PATIENTS

Type of Tumor	*Total*	*Male*	*Female*	*Youngest Patient*	*Oldest Patient*
Total	88	50	38	13 mo male	79 male
Tumors of skin	33	14	19	26 male (melanoma)	74 male (squamous carcinoma)
Tumors of soft somatic tissues	47	33	14	13 mo male (rhabdomyosarcoma)	79 male (fibrosarcoma)
Tumors of bone	8	3	5	11 female (metastatic neuroblastoma)	67, female (osteogenic sarcoma)

4 Many bone sarcomas proximal to the elbow Periosteal sarcomas scleros ing osteosarcomas others of low-grade *malignancy those well confined to the* bone and those involving the lower half of the humerus may be treated by more conservative amputations at the discre-tion and experience of the operator But the majority of the other bone sarcomas *particularly those involving the* upper end of the humerus those extending up-ward though the entire medullary cavity and those which have extended beyond the confines of the bone to infiltrate surrounding normal tissues are more suitable for interscapulothoracic ampu tation

5 The rule of Halstead and Corner that the amputations should be per formed above the proximal attachments

and the occasional lymphosarcomas which extend beyond the lymph nodes to involve the surrounding soft tissues In the case of these latter two tumors, preliminary radiation therapy is usually the procedure of choice Encapsulated malignant neurilemmomas liposar comas and rhabdomyosarcomas may be successfully treated in some instances by radical dissection of the muscle groups containing these tumors, with preserva tion of the extremity

8. Inoperable axillary tumors adherent to blood vessels brachial plexus shoul der joint, and muscles, permitting no at tempts at local excision however radical

9 Sarcomas of the clavicle or scapula Interscapulothoracic amputation is indi cated for these tumors only when the location of the sarcomas is so intimate

to the shoulder joint that partial or complete scapulectomy or resection of the clavicle would not be possible or feasible, especially if the arm is useless and painful. The entire scapula may safely be removed without too great disability and with preservation of the arm if involved by chondrosarcoma or osteosarcoma of low-grade malignancy.

10. Relatively benign tumors causing symptoms and disability because of their size and location, *e.g.*, certain huge chondromas developing in the neighborhood of the shoulder joint.

TABLE 22. TYPE OF TUMOR AND END RESULTS FOLLOWING INTERSCAPULOTHORACIC AMPUTATION

Type of Malignant Tumor	*Total Cases*	*Patients Who Have Died*			*Patients Who Are Living*				
							Without Cancer		
		Total Cases	*With Cancer*	*Without Cancer*	*Total Cases*	*With Cancer*	*Under 5 Yr.*	*5–10 Yr.*	*Over 10 Yr.*
Total cases	88*	58†	51	4	29	5	11	8‡	5§
Tumors, primary in the extremity—*Total*	81	53	47	3	28	4	11	8	5
Tumors of skin	26	19	17	1	7	2	3	2	0
Tumors of soft somatic tissues	47	29	25	2	18	2	5	6	5
Tumors of bone	8	5	5	0	3	0	3	0	0
Tumors of the skin, primary elsewhere‖	7*	5	4	1	1	1	0	0	0

* Total includes one patient lost to follow-up.

† Total includes 3 patients in whom the cause of death was not known: 1 melanoma and 2 tumors of soft somatic tissues.

‡ Living without cancer 5–10 yr.: melanoma 1, carcinoma 1, fibrosarcoma 3, synovioma 1, reticulum-cell sarcoma 1, angiosarcoma 1.

§ Living without cancer over 10 yr.: rhabdomyosarcoma 1, tumors of peripheral nerves 2, sarcoma unclassified 1, fibrosarcoma 1.

‖ Primary site: eye 1, unknown 1 for melanoma. Carcinoma: breast 3, colon 1, alveolar ridge 1.

OPERATIVE TECHNIC

A. THE CLASSIC BERGER OPERATION

The patient is placed on his back with the involved shoulder elevated so that the skin can be prepared by antisepsis well beyond the midline, front and back. The corresponding arm is well wrapped from fingers to shoulder and left free and mobile to be held by an assistant. By this method the arm may be held in various positions to facilitate the anterior or posterior dissection of the shoulder. Tourniquets and Wyeth pins are unnecessary.

A linear incision is first made over the middle third of the clavicle, and this incision is extended through the soft tissues to the periosteum. The middle third of the clavicle is now resected, usually with a Gigli saw. Through this window the subclavian vessels are exposed, with the artery more deeply situated beneath the vein. At this point the modification of LeConte may well be given, as he advo

Fig. 63. Incision for preliminary division of clavicle for ligation of axillary vessels and exposure of brachial plexus. Insert shows skin incision (Pack, McNeer and Coley Surg Gynec. & Obst. 74 161 1942. *Courtesy* Surgery Gynecology and Obstetrics.)

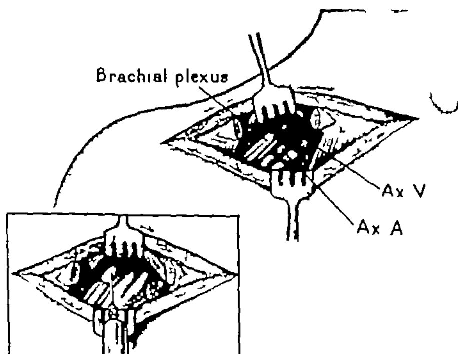


Fig. 62a. Exposure and preliminary ligation of the axillary artery and vein by the Berger technic. We prefer the Kocher exposure (see Fig. 71) (Pack, McNeer and Coley Surg. Gynec. & Obst. 74 161 1942. *Courtesy* Surgery Gynecology and Obstetrics.)

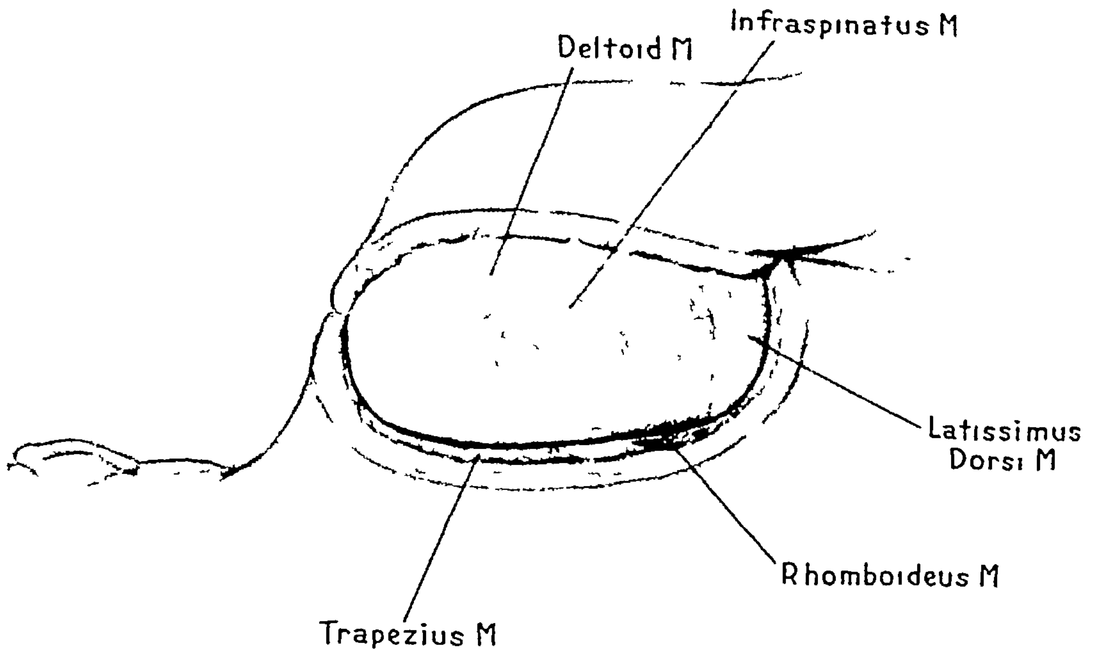


FIG 63 The incision carried posteriorly shows the muscles attached to the scapula (Pack, McNeer, and Coley, Surg Gynec & Obst 74 161, 1942 *Courtesy*, Surgery, Gynecology and Obstetrics)

cates the resection of the entire clavicle, beginning with the sternoclavicular joint, for the avowed reason that this procedure affords a better exposure of the subclavian vessels, particularly the artery which is to be ligated first, and enables the operator to recognize and ligate the suprascapular and transverse cervical vessels This complete claviculectomy does give better exposure and is absolutely indicated if the clavicle is involved by the tumor, but it must be admitted that there are greater dangers of air embolism and injury to the pleural dome and thoracic duct (on the left side)

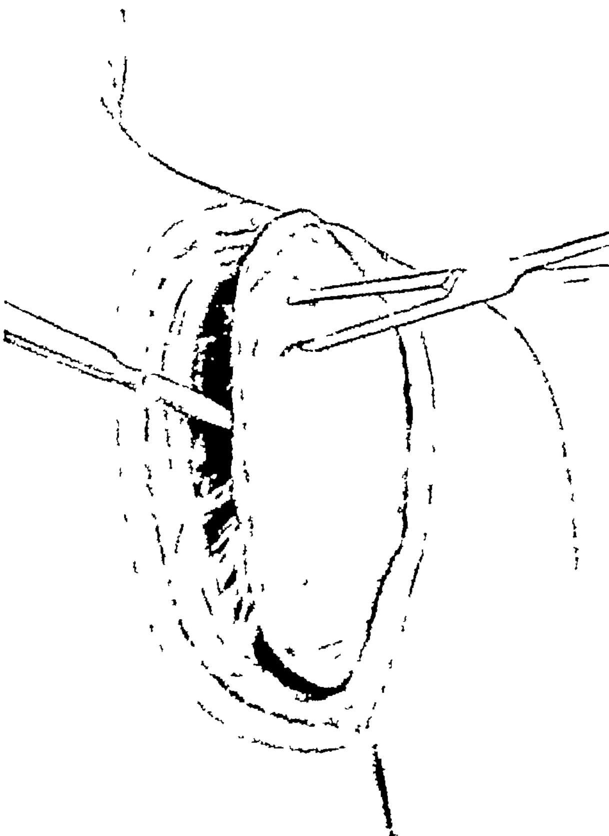


FIG 64 Vorsellum grasping scapula near the vertebral border and beneath it (subscapularis muscle) (Pack, McNeer, and Coley, Surg Gynec & Obst 74 161, 1942 *Courtesy*, Surgery, Gynecology and Obstetrics)

After exposure of the neurovascular bundle at the base of the neck, the subclavian artery is divided between ligatures of heavy black silk, and the vein is treated in a similar manner The proximal stump of the artery and vein are always doubly ligated The original skin incision is then carried almost to the tip of the acromion, after which it is extended downward along the anterior axillary border The arm is then drawn across the body, and the posterior flap is outlined by an incision of the skin along the vertebral border of the scapula, which unites with the anterior incision along the lateral axillary border The arm is then swung back to its original

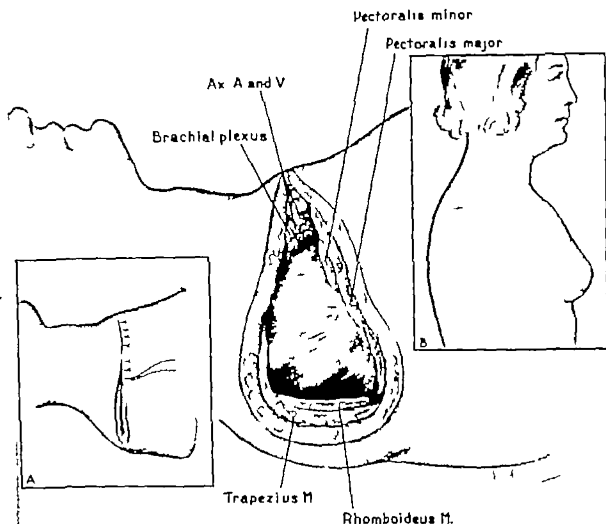


FIG. 65 Wound ready for closure. Inserts demonstrate transverse linear scar (Pack, McNeer and Coley Surg Gynec. & Obst. 74 161 1942 *Courtesy* Surgery Gynecology and Obstetrics.)

position, and the anterior incision is deepened as far as the pectoral muscles Division of the pectoral muscles now gives excellent exposure of the brachial plexus The surface of the plexus is painted with 10 per cent cocaine and/or 2 per cent Novocain solution is injected into the nerve trunks After division of the various nerve components of the plexus the ligated proximal stumps are injected with small quantities of 95 per cent alcohol to lessen the possibility of amputation neuromas and causalgia. The arm is now brought forward again, and the muscles of the posterior flap along the vertebral margin of the scapula, are divided. Care is taken to clamp sever and ligate the transverse cervical artery before it retracts, if this has not been done at an earlier stage With the scapula freed of its muscular attachments the amputation is complete The bleeding vessels are ligated with fine silk. The skin can usually be closed with interrupted black silk sutures It heals with a surprisingly good linear scar Since the adoption of the silk technic, there has been less need for the use of drains Skin-grafting is resorted to in instances in which the size and location of the tumor and the degree of skin involvement require a greater sacrifice of skin

The patient is usually able to be out of bed on the third postoperative day and at home within two weeks

B THE ANTERIOR OR PECTORAL APPROACH OF KOCHER

The only difficulty encountered during the Berger operation is the exposure



Fig 66 (*Left* and *right*) Operative specimen of amputated hand and forearm Note congenital neurogenic contractures of fingers associated with localized neurofibromatosis of this extremity Multiple malignant neurilemmomas appeared, first of hand, later of forearm (see cut), later of upper arm, and finally of shoulder, necessitating interscapulothoracic amputation (Pack, McNeer, and Coley, Surg Gynec & Obst. *74* 161, 1942 *Courtesy*, Surgery, Gynecology and Obstetrics)

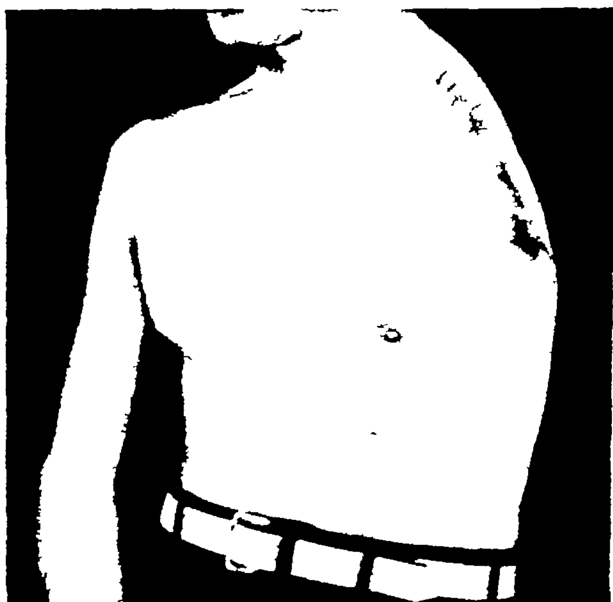


Fig 67 To illustrate the anatomic defect and character of the scar The patient is now living and well more than 20 years following the forequarter amputation (Pack, McNeer, and Coley, Surg Gynec & Obst. *74* 161, 1942 *Courtesy*, Surg Gynec & Obst)

of the subclavian vessels The anterior approach of Kocher (Fig 71) avoids this handicap and in our hands has proved to be a welcome modification of the original operation After the middle third or the entire clavicle has been resected, the ligation of the subclavian vessels is postponed until the anterior incision is carried through the pectoral muscles into the axilla This part of the dissection is similar to the same phase in a radical mastectomy, as the axillary artery and the vein come immediately into view With the more adequate exposure afforded by enlargement of the operating field, the subclavian vessels are more readily located, and the underlying artery is mobilized and ligated without the previous hazard of injuring the overlying vein From this point on,

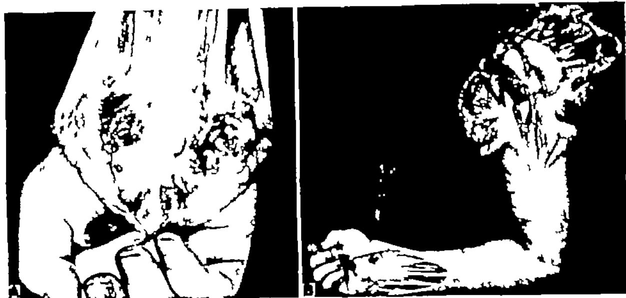


Fig. 68. A. Surgical specimen from an interscapulothoracic amputation combined with a lower (supraclavicular) neck dissection. Synovioma involving the flexor tendons of the wrist with metastases to the lymph nodes of the axillary and supraclavicular spaces. *B* The surgical principle of exarticulation of an extremity combined with excision of the regional lymph nodes is clearly indicated in this case This type of tumor rivals melanoma in its malignant propensities. (Pack, Ehrlich, and Gentil, Surg Gynec. & Obst. *84* 1105 1947 *Courtesy* Surgery Gynecology and Obstetrics.)



Figs. 69 and 70 (*Left*) A bulky diffuse synovial sarcoma involving the shoulder joint. (*Right*) Same patient following an interscapulothoracic amputation. (Pack and Ariel, Surgery 28 1047 1950)

the operative technic is exactly similar to that described above.

C. THE POSTERIOR OR RETROSCAPULAR APPROACH OF LITTLEWOOD

According to some advocates particularly Knaggs the posterior approach of Littlewood may be done with greater speed and more anatomic exactness After division of the midthird or entire clavicle, the posterior flap is outlined first, and then the scapula is freed from its medial and superior muscular attachments The advantage of this technic is that, when the neurovascular bundle is

TABLE 23 TYPE OF TUMOR AND END RESULTS FOLLOWING INTERSCAPULOTHORACIC AMPUTATION

		Patients Who Have Died			Patients Who Are Living				
							Without Cancer		
Type of Tumor	Total Cases	Total Cases	With Cancer	Without Cancer	Total Cases	With Cancer	Under 5 Yr	5–10 Yr	Over 10 Yr
TUMORS OF SOFT SOMATIC TISSUES									
Total cases	47	29	25	2	18	2	5	6	5
Rhabdomyosarcoma	14	11	10	0	3	0	2	0	1
Fibrosarcoma	8	2	1	1	6	1	1	3	1
Synovioma	7	5	5	0	2	1	0	1	0
Sarcoma unclassified	6	5	4	1	1	0	0	0	1
Malignant neurilemmoma	5	3	2	0	2	0	0	0	2
Angiosarcoma	4	3	3	0	1	0	0	1	0
Reticulum-cell sarcoma	1	0	0	0	1	0	0	1	0
Liposarcoma	1	0	0	0	1	0	1	0	0
Extraabdominal desmoid tumor	1	0	0	0	1	0	1	0	0
TUMORS OF THE SKIN, PRIMARY IN THE EXTREMITY									
Total cases	26	19	17	1	7	2	3	2	0
Melanoma	20	15	14	0	5	1	3	1	0
Carcinoma	6	4	3	1	2	1	0	1	0
TUMORS OF BONE									
Total cases	8	5	5	0	3	0	3	0	0
Osteogenic sarcoma	3	2	2	0	1	0	1	0	0
Chondrosarcoma	2	2	2	0	0	0	0	0	0
Neuroblastoma	1	1	1	0	0	0	0	0	0
Reticulum-cell sarcoma	1	0	0	0	1	0	1	0	0
Myeloma	1	0	0	0	1	0	1	0	0

encountered from the posterior aspect, the subclavian artery appears first, the vein second, and the brachial plexus last, in the exact order desired for ligation and severance

D. ADDITIONAL OPERATIVE DETAILS

Cairo (1924) suggested a two-stage operation in old patients, first disarticulating the humerus and performing the scapulectomy later LaFaye did not resect the clavicle but ligated the axillary vessels and disarticulated the humerus and the scapula from the clavicle Kuster added a vertical incision over the sternomastoid muscle to the handle of the racquet incision along the clavicle He asserted that this gave a better exposure of the subclavian vessels and that it was particularly helpful in permitting primary ligation of the transverse cervical artery and vein

TABLE 24 PREVIOUS TREATMENT IN RELATION TO END RESULTS AFTER INTERSCAPULOTHORACIC AMPUTATION FOR TUMORS PRIMARY IN THE EXTREMITY

(The Memorial Center and the Pack Medical Group)

Type of Previous Treatment	*All Cases*			*Tumors of Skin*			*Tumors of Soft Somatic Tissues*			*Tumors of Bone*		
	Total	*Died*	*Living*	*Total*	*Died*	*Living*	*Total*	*Died*	*Living*	*Total*	*Died*	*Living*
All cases	81	53	28	26	19	7	47	29	18	8	5	3
No previous treatment	19	12	7	4	4	0	11	6	5	4	2	2
Irradiation only	5	4	1	1	1	0	4	3	1	0	0	0
Excision*	38	25	13	13	9	4	22	14	8	3	2	1
Dissection†	8	4	4	4	2	2	4	2	2	0	0	0
Amputation‡	11	8	3	4	3	1	6	4	2	1	1	0

* Excision only	22
Excision & irradiation	16
† Dissection & excision	6
Dissection, excision, & irradiation	1
Dissection & irradiation	1
‡ Amputation only	3
Amputation & excision	2
Amputation, excision, & irradiation	2
Amputation, dissection, & irradiation	2
Amputation, excision, & dissection	1
Amputation & dissection	1

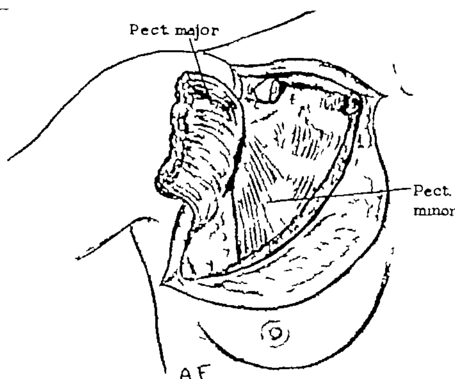


FIG. 71 Clavicle transected by the anterior pectoral approach of Kocher Pectoral muscles being dissected free of chest wall. Breast reflected downward, permitting excellent exposure of the axillary vessels and nerves.

COMPLICATIONS

Interscapulothoracic amputation is a radical, major, and dramatic operation, but it is really a simple and safe procedure once the subclavian vessels are securely ligated The exposure of these vessels is occasionally very difficult due to the location of certain bulky tumors which overlie the operative field In thin-chested individuals, especially when the arm has long been useless, the subclavian vessels as they lie on the first rib must be looked for considerably above the clavicular incision

With the danger of hemorrhage avoided, the patient subjected to this operation is relatively safe In one of our recent patients, the subclavian vein was accidently opened during a difficult attempt to free the artery, air was audibly aspirated into the vein, hemorrhage, although great, was controlled by compressing the vein with a finger against the first rib, and the patient went into shock He was restored by immediate transfusion as the vein was repaired, and the operator was allowed to proceed with the amputation The patient recovered from this experience without any late complications One of von Bergmann's patients died from hemorrhage caused by extension of the cancer around the subclavian vessels, this surgeon made a heroic effort to save his patient by tying off the superior vena cava

Shock is minimal when proper preoperative and sustaining measures are in use, such as blood transfusions, usually given concurrently during the operation, in the opposite arm or leg Due to fixation of the tumor, the pleural cavity may be entered with the complications characteristic of pneumothorax Injury to the thoracic duct by a left interscapulothoracic amputation may conceivably occur, but we have never seen or read of this occurrence

CONSERVATIVE OPERATIONS VERSUS INTERSCAPULOTHORACIC AMPUTATION FOR MALIGNANT TUMORS

In the listing of indications for interscapulothoracic amputation, the values of this radical procedure as compared with more conservative operations have been considered The practicability of the irradiation of certain liposarcomas and lymphosarcomas and of the dissection of muscle groups containing encapsulated rhabdomyosarcomas and neurilemmomas of low-grade malignancy is recognized

In selecting one of these more conservative procedures, such as scapulectomy or disarticulation of the humerus, the surgeon should do so in the firm belief that it is wholly sufficient as far as the local tumor is concerned and not because he relies on another opportunity for local cure through a secondary or subsequent interscapulothoracic amputation

ADVANTAGES OF INTERSCAPULOTHORACIC AMPUTATION OVER DISARTICULATION FOR MALIGNANT TUMORS OF THE UPPER ARM

The following advantages of interscapulothoracic amputation over disarticulation for malignant tumors of the upper arm may be mentioned

1 The lymphatics and veins are removed at a much higher level

2 The shoulder muscles with their natural fascial planes are entirely re-

TABLE 25 FIVE YEAR END RESULTS FOLLOWING INTERSCAPULOTHORACIC AMPUTATION FOR TUMORS PRIMARY IN THE EXTREMITY IN RELATION TO METASTASIS FOUND AT OPERATION

	All Cases			*Tumors of Skin*			*Tumors of Soft Somatic Tissues*			*Tumors of Bone*		
		Metastasis			*Metastasis*			*Metastasis*			*Metastasis*	
End Result	*All Cases*	*Present*	*Absent*	*All Cases*	*Present*	*Absent*	*All Cases*	*Present*	*Absent*	*All Cases*	*Present*	*Absent*
Determinate cases	39	14	25	9	7	2	28	6	22	2	1	1
Failures died with cancer	26	12	14	7	7	0	17	4	13	2	1	1
Successful results living without cancer	13	2	11	2	0	2	11	2	9	0	0	0

TABLE 26 END RESULTS OF INTERSCAPULOTHORACIC AMPUTATION FOR METASTATIC TUMORS WITH PRIMARY TUMOR NOT IN THE EXTREMITY

		Primary Tumor		*Metastatic Tumor*			
Sex	*Age*	*Location*	*Histologic Type*	*Location*	*Previous Treatment*	*Date of Radical Surgery*	*End Results*
M	57	Choroid	Melanoma	Arm	Excision	9-3-41	Died with cancer 5 mo
F	42	Breast	Adenocarcinoma	Supraclavicular region	Irradiation	4-27-49	Died with cancer 8 mo
F	43	Breast	Adenocarcinoma	Axilla	None	4-22-49	Died with cancer 10 mo
F	45	Colon	Adenocarcinoma	Axilla	Excision 2 axillary dissections	5-28-51	Died with cancer 23 mo
F	33	Not known	Melanoma	Axilla	Excision	8-23-51	Lost to follow-up soon after operation
M	55	Alveolar ridge	Squamous carcinoma	Shoulder	None	12 10-51	Died in 12 mo from perforated gastric ulcer No evidence of cancer at that time
F	61	Breast	Adenocarcinoma	Arm	None	5-28-52	Living 14 mo postoperatively with metastases to spine

TABLE 27 PATIENTS SURVIVING FIVE YEARS OR MORE WITHOUT CANCER FOLLOWING INTERSCAPULOTHORIC AMPUTATION

Sex	*Age*	*Previous Treatment*	*Location of Primary Tumor*	*Date of Operation*	*Histologic Type of Tumor*	*Living without Cancer*
M	24	3 local excisions 3 amputations and axillary dissection	Forearm	2-25-35	Malignant neurilemmoma	20 yr
M	34	Irradiation	Arm	3-2-38	Neurofibrosarcoma	17 yr
M	47	2 local excisions Irradiation	Axilla	9-27-39	Paraganglioma	15 yr 6 mo
M	30	4 local excisions Irradiation	Arm	11-8-39	Sarcoma unclassified	14 yr
F	48	Local excision Irradiation	Arm	4-7-41	Rhabdomyosarcoma	14 yr
F	43	2 local excisions	Axilla	10-31-41	Fibrosarcoma	Over 9 yr
F	28	None	Shoulder	2-21-45	Synovioma	10 yr
M	10	None	Axilla	5-14-45	Fibrosarcoma	10 yr
F	27	2 local excisions	Infraclavicular region	3-11-46	Fibrosarcoma	9 yr
M	21	Local excision	Arm	9-10-46	Reticulum-cell sarcoma	8 yr 5 mo
F	57	3 local excisions Irradiation	Axilla	8-18-47	Basal-cell carcinoma	7 yr 4 mo
M	47	Local excision Irradiation	Axilla	9-3-47	Melanoma	7 yr 5 mo
M	14	Local excision	Axilla	11-28-47	Angioendothelioma	7 yr 4 mo

TABLE 28 FIVE-YEAR END RESULTS FOLLOWING INTERSCAPULOTHORACIC AMPUTATION FOR MALIGNANT TUMORS PRIMARY IN THE EXTREMITY

End Results	*All Cases*	*Tumors of Skin*	*Tumors of Soft Somatic Tissues*	*Tumors of Bone*
All cases 1926–1953	81	26	47	8
Indeterminate cases—*Total*	6	2	4	0
Cause of death not known	3	1	2	0
Died of other causes	3	1	2	0
Determinate cases, 1926–1953	75	24	43	8
Determinate cases, 1949–1953	36	15	15	6
Determinate cases, 1926–1948, for evaluating 5-yr -cure rate	39	9	28	2
Failures, died with cancer	26	7	17	2
Successful results, living without cancer over 5 yr	13	2	11	0
End results				
Successful results divided by the determinate cases, 1926–1948	13/39 (33 3 per cent)	2/9 (22 2 per cent)	11/28 (39 3 per cent)	None

moved, which is especially important if the tumor has shown invasive tendencies

3 The more radical operation not only permits dissection of the axilla but a removal of the axillary boundaries

4 The mortality is no greater The interscapulothoracic amputations reported here were done without an operative death, which is proof enough of the safety of this operation.

5 The wounds resultant after interscapulothoracic amputation heal more satisfactorily as there are practically no dead spaces to be obliterated

6 The deformity is greater but not enough to be a deciding factor

7 Interscapulothoracic amputation is often done for a malignant tumor recurrent in the stump of a disarticulation This very fact would indicate that the original disarticulation had not been wisely chosen as the proper (
Consecutive operations finally
ing in interscapulothoracic ar
appear in every reported serie
ing our own A patient with a r
neurilemmoma or fascial sarcoi
hand, wrist, or forearm relates
of one or more local excisions
currences developing each time
to the scar finally amputatic
forearm, later of the arm and
disarticulation of the humeru:
done for proximally recurring
usually with increasing degrees
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events occurs, few surgeons v
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CHAPTER 14

Radiation Therapy of Tumors of the Soft Somatic Tissues

RADIOSENSITIVITY OF SOFT TISSUE TUMORS

It is assumed that any tumor selected for treatment by irradiation possesses some degree of radiosusceptibility Failure to consider this premise has led to the injudicious use of these physical agents with consequent loss of confidence in their effectiveness The tumor benign or malignant, must be more radiosensitive than the normal tissues which contain it, else radium and x rays could offer no advantages over any destructive, non selective cautery The radiologist should decide, if possible, whether his therapeutic efforts are to be curative or palliative, inasmuch as different biologic and physical principles are involved. He also realizes that *radiosensitivity* and *radiocurability* are not synonymous some highly radiosensitive tumors may become a generalized or systemic disease early in their course, whereas other more radioresistant tumors, metastasizing late, are radiocurable by slow progressive radiation fibrosis.

Radiologists and biophysicists interested in radiation therapy have long known that any tissue irradiated possesses cells which vary in their susceptibility to treatment by any wavelength of radiation. In epidermoid carcinoma, for example the variation in responsiveness is in the magnitude of one to three, *i.e.*, the most radiosensitive carcinoma cells in the epidermoid carcinoma may respond with one-third the dose that is necessary to destroy the most radioresistant cells in that specific cancer This being true, one should give a dose of irradiation sufficiently great to destroy the most radioresistant component of the squamous-cell carcinoma, not just enough to cause temporary clinical regression. The same condition obtains for sarcomas of the soft tissues, only more so There is an infinitely greater disparity between the cells of the sarcomas of soft tissues which are quite radiosensitive and those which are very radioresistant. The order of magnitude of disparity here as regards radiosensitivity may be one to six or one to eight. The most radiosensitive part of the sarcoma may completely disappear and the radioresistant part be so minute in quantity as not to be palpable by the clinician, and yet, on subsequent surgical excision residual active sarcoma cells are microscopically discovered This has been one of the prime handicaps which have militated against successful irradiation of sarcomas of the soft somatic

tissues The radiosensitivity of the different sarcomas may be tabulated as follows

1 *Granulation-cell sarcoma* Very radiosensitive

2 *Liposarcoma* The embryonal liposarcoma is often very radiosensitive Complete clinical disappearance, however, does not necessarily indicate sterilization of the sarcoma The metastases are usually more sensitive than the primary tumor

3 *Kaposi's multiple hemorrhagic sarcoma* Comparatively radioresistant However, radiation therapy offers the best method of control whenever the tumors are so diffuse or multiple as to preclude surgical excision

4 *Angiosarcoma* This tumor is extremely variable in its radiosensitivity The inoperable lesions are sometimes controlled satisfactorily, but palliatively, by irradiation, and the resectable angiosarcomas are sometimes best managed by heavy preoperative irradiation prior to radical surgical excision

5 *Desmoid tumor of abdominal wall* The desmoid tumor is fibrous and radioresistant Direct x-ray therapy exercises only growth restraint, and interstitial irradiation is contraindicated We have witnessed phenomenal regression with control for years of recurrent inoperable desmoid tumors following x-ray castration, we have assumed this to be a hormonal effect These tumors receive a tremendous growth impetus during pregnancy

6 *Fibrosarcoma (fascial sarcoma)* Most radioresistant of all malignant soft part neoplasms Paradoxically, x-ray therapy is quite effective because it induces progressive fibrosis and shrinkage of the tumor with indeterminate but often prolonged growth inactivity Surgical treatment is preferable, of course, but the inoperable extensive fibrosarcomas have been controlled by irradiation for periods as long as 5 to 15 years

7. *Lymphangioma* In our experience this tumor has never responded to the best-planned irradiation

8 *Hemangioma.* The port-wine s is not easily obliterated by x-rays radium Hemangiomas with an art component have physical qualities i tating against a worthwhile respons radiation therapy The systemic hen gioma involving a complete extrei and incorporating even muscles bone is notoriously radioresistant operable hemangiomas of bone (e cially vertebrae) and liver are succ fully treated by high-voltage x therapy In the early months of infa the cavernous hemangiomas are i radiosensitive As the child grows ol the endothelial cells and delicate p vascular tissues of the tumor lose t embryonal qualities and become n adult in character and correspondi more radioresistant These comm concerning the radiosensitivity of mangiomas do not imply approval of choice of irradiation for treatment. indications for treatment will be sidered under the section dealing tumors of the vascular system

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12. *Wilms's embryonal adenomyosarcoma* This tumor is known to be sensitive to irradiation essentially because of extensive vascularity with widely distended capillaries which can be destroyed by irradiation and because of its rapid cell division However with improved surgical technic and a better understanding of the natural history of the disease, this tumor although radiosensitive is best treated by a combination of surgical extirpation and postoperative irradiation Preoperative irradiation, which is still given by many physicians, has been shown to be of questionable or no value by Gross who reports a series of patients whose mortality increased significantly when given preoperative irradiation He was definitely of the opinion that it was detrimental and abandoned its use However excellent results are obtained with postoperative irradiation as noted by the significant improvement in the rate of cures obtained at the Boston City Hospital when that institution started using postoperative irradiation. Irradiation is commenced on the day of operation two to three portals are outlined over the renal bed and fractionated irradiation utilizing cross fire technic is employed. The factors are 200–250 kv half value layer of 1–1½ cm. of copper 200–250 r to one port each day until a total dose of 1200–1550 × 3 has been administered. Recurrent tumors and metastases respond very well to external irradiation and great palliation is offered these patients

METHODS OF RADIATION THERAPY OF SOFT TISSUE TUMORS

Radon Bulb

The radon bulb is a small, radon filled glass bulb on the end of a long applicator The bulb is 4 mm in diameter has no filtration except glass, and therefore emits both beta and gamma rays It is useful by topical contact application in the treatment of punctate hemangiomas and the small, discrete skin nodules of Kaposi's hemorrhagic sarcoma. A dose of from 100 to 400 mc. minutes usually suffices to cause good regression.

Radium Applicators for Skin Use

A series of radium applicators are available for the treatment of superficial neoplasms, either intracutaneous or subcutaneous Discrete foci of Kaposi's hemorrhagic sarcoma offer the chief opportunity for the use of this modality These applicators have been commonly employed for the treatment of cutaneous hemangiomas, although effective and immediately satisfactory the late sequelae and complications have made this method of therapy increasingly unpopular

These radium applicators may be used in the form of a plaque or moulage The floor of the plaques (filter) consists of 2.0 mm of brass with either 0.2 mm. platinum or 0.5 gold added depending on the radium capsules used within the box plaque The radium-skin distance is 1 cm. for the smaller applicators and 3 cm for the tray, which is used when a larger surface is irradiated and a greater depth dose is desired This distance is obtained by an interposed block of balsa wood or Bakelite The surface dimen

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METHODS OF RADIATION THERAPY OF SOFT TISSUE TUMORS

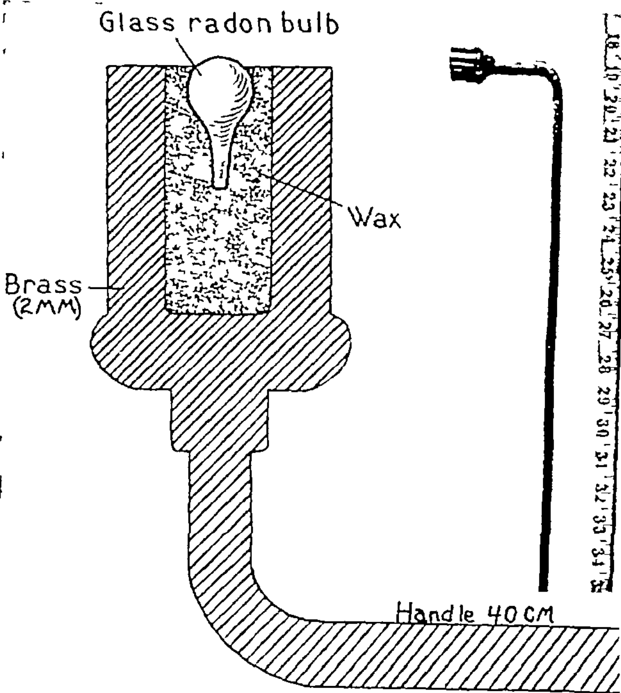
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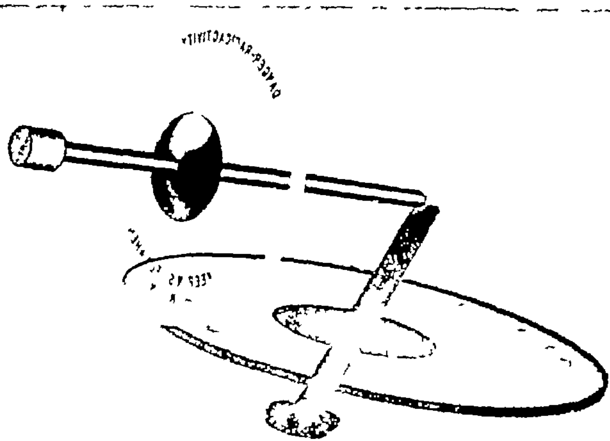


FIG 72 (*Upper*) Radon bulb for external beta irradiation This instrument has been extensively employed in the past and is still used where radon emanation plants supply the radon as the source of the beta rays (*Lower*) Beta irradiator which utilizes the radioactive isotope of strontium (Sr^{91}) as its source for beta rays

sions, shapes, and dosages are given in Table 29

INTERSTITIAL IRRADIATION

For interstitial irradiation of angiomatous masses, a small, radon-filled capillary gold seed 4 0 mm. in length (filter, 0.2 mm. Au) is inserted with special hollow trocar needles These gold seeds contain ¾ to 1½ mc of radon and are inserted well below the surface of the tumor and at least 2 cm apart. Only a few radon seeds in the center of the angioma are needed to initiate the thrombosis through which obliteration of the tumor occurs

More than a decade ago it was a frequent practice to treat sarcomas of the soft tissues (particularly recurrent and inoperable neoplasms) by interstitial irradiation, using either gold radon seeds as point sources or radium needles as linear sources of radiation. Previous biophysical studies had provided data enabling the radium therapist to deliver the requisite number of threshold erythema doses per cubic volume of tumor theoretically necessary for a lethal dose Unfortunately, even the most accurate interstitial irradiation has usually resulted in failure for several reasons: (1) the technical difficulty of accurate placement of seeds or needles throughout a tumor mass in such a way as to secure

TABLE 29 RADIUM APPLICATORS USED IN THE TREATMENT OF SUPERFICIAL SOMATIC TISSUE TUMORS

Type	*Size*	*Area Radiating Surface*	*Filter*	*Distance*	*Dose (mgh)*
Square plaque	1 8 cm square	2 sq cm	2 mm brass + 0 2 mm Pt	1 cm	500-1000
Long plaque	2 7 × 1 7 cm	3 75 sq cm	2 mm brass + 0 2 mm Pt	1 cm	600-1200
Round plaque	4 cm diameter	7 sq cm	2 mm brass + 0 2 mm. Pt	1 cm	1000-1600
Tray	6 2 cm diameter	17 5 sq cm	2 mm brass + 0 2 mm Pt	3 cm	2000-4000

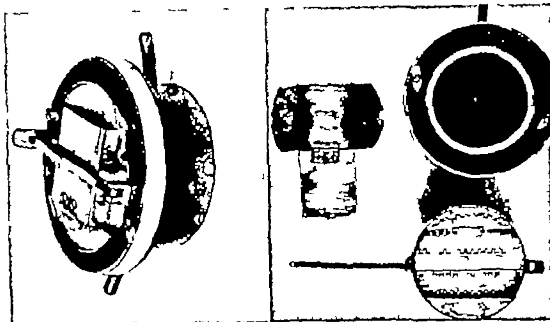


FIG. 73. Radium tray for use at 3 cm. distance from the skin. The instrument is photographed assembled and dissembled, to show the arrangements for the platinum radium cells. The accessory small brass box on the cover is for supplementary radium. (Pack, A. M. A. Arch. Surg 33-940 1936)

relatively uniform distribution of radiation dosage and effect, (2) the majority of soft part sarcomas are so bulky that it would be impossible to deliver a cancericidal dose of irradiation from interstitial sources alone (3) the limits or extension of the unencapsulated soft part sarcomas are so uncertain that survival of the peripheral segments only too often follows attempts at interstitial irradiation (4) disastrous complications may occur such as liquefaction necrosis infection ulceration and fungation of tumor and (5) pulmonary metastases can develop within a short time after the employment of interstitial irradiation We have observed numerous instances of this and have naturally inferred that the trauma of multiple punctures through such highly malignant tumors has contributed to such dissemination Although it is possible occasionally to control small sarcomas by this method, the procedure is too dangerous and uncertain It is decidedly inferior to surgical excision and we have therefore abandoned it

LOW VOLTAGE CONTACT X RAY THERAPY

In the treatment of Kaposi's hemorrhagic sarcoma of the skin dermal lymphangiosarcomas cutaneous metastases of embryonal liposarcoma, and carefully selected cutaneous hemangiomas (exclusive of face, hands and feet) special x ray equipment permits superficial irradiation of the tumors without injury to the surrounding tissues

CHAOUL CONTACT OR SHORT DISTANCE ROENTGEN THERAPY

During the past 25 years physicists and radiologists devoted considerable attention to the construction of low voltage x ray machines which combined the advantages of radium dose distribution as used for surface application and the economy efficacy and convenience of x rays. Special x ray tubes furnishing a dose distribution similar to contact or superficial radium therapy were designed many years ago and then abandoned because of technical difficulties concerned with the prevention of shock to the patient These difficulties were subsequently overcome when the short distance or contact x ray method was developed In 1929 Schaefer and Witte of Gottingen, Germany experimented in using a Lenard tube and later added a metal filter over the tube which did not

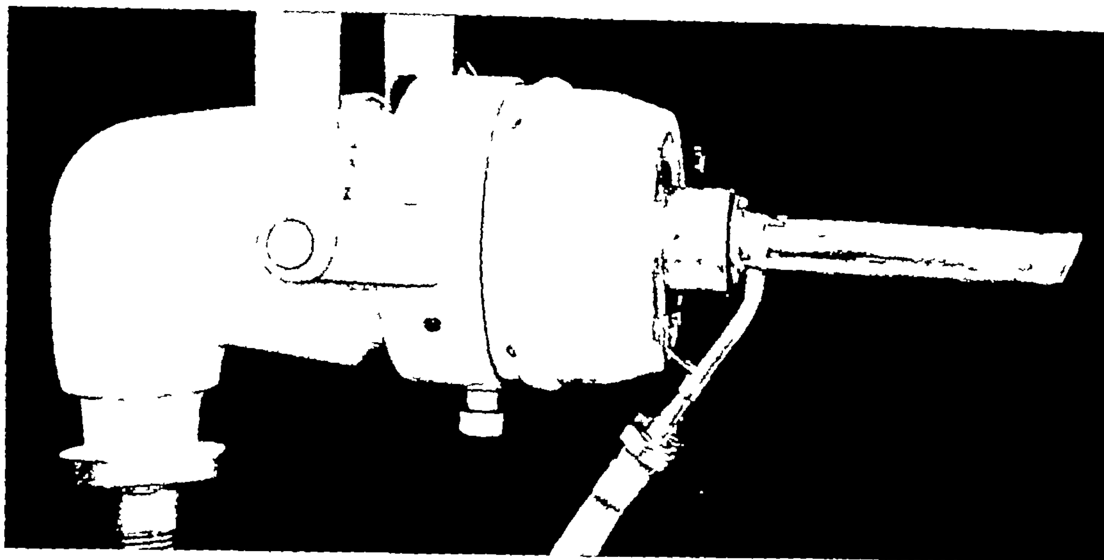


Fig 74 The cone of Chaoul apparatus contact or short-distance x-ray therapy apparatus Transmission anode

permit the emergence of a cathode beam and served as the anode or target The thin copper filter or transmission anode was planoconcave or planoconvex to modify the shape and focal sharpness of the emergent beam Chaoul, of the Charite Surgical Clinic, Berlin, designed a *similar apparatus for low-voltage short-distance* or contact x-ray therapy which was limited to a voltage range of 50 to 60 kv with a filtration of 0 2 mm of copper The anode is so placed that the tube operates with contact or from 3 to 5 cm target-skin distance There are applicators or cones of various sizes and shapes to be placed against the lesions

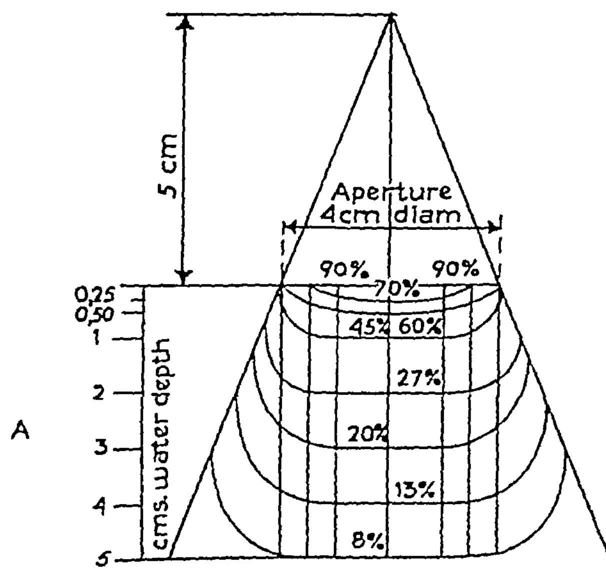


Fig 75 Isodoses chart with 5 cm. T S D 60 kv, filter 0 2 mm Cu, aperture of applicator, 4 cm diameter

to be treated The Chaoul machine water-cooled and shockproof With tl apparatus it is possible to deliver the peutic doses to the tumor sufficie to disintegrate tumor cells and yet spare the surrounding tumor bed l using small fields sharply localized abo the tumor It furnishes limitation depth effect by producing a steep ener gradient so that the rays are absorb in the superficial tissues For conta application, the dose of emission is a proximately 800 r per minute, for target-skin distance of 3 cm, it is 88 per minute, for a target-skin distance 5 cm, it is 36 r per minute This instr ment has only a specialized use, *i e*, the treatment of superficial tumors the skin The reaction is sharply circum scribed around the cancer

Philips Contact Roentgen Ray Apparatus

This is a flexible and serviceable uni contained in a small portable cabinet and can be used in any roo tains an outlet for 110 vo current A shockproof fle meters i nnects tube t he axially te and sh of only

tional filtration is deemed necessary disks of aluminum 1.0 or 2.5 mm. thick may be inserted over the tube. The diameter of the emergent x ray beam is slightly less than 2 inches If the surface dimensions of the tumor are greater then the lesion is divided into multiple fields or ports The total target-contact is 2 cm. The intensity is always 50 kv constant potential. The advantage is in the roentgen output of the Philips tube. Its output is so great that only a very short time is necessary to complete any treatment. The total dose administered for skin tumors varies from 1500 r units to 5000 or 6000 r units as in the case of Kaposi s hemorrhagic sarcoma.

HIGH VOLTAGE ROENTGEN THERAPY

For sarcomas of the trunk and extremities which are incurable or inoperable and for which irradiation is selected for palliation, the following factors are generally employed 250 kv filter 1.5 mm. copper target skin distances of 50 to 70 cm., and either open ports or fields delineated for the use of cones If the sarcoma is located so that cross firing through multiple fields is possible, a greater tumor dose can be delivered with correspondingly better tumor regression and growth restraint. In general, the following principle may be applied. If the sarcoma is of a radiosensitive type, large daily fractions of from 300 to 400 r can be given If the sarcoma is radioresistant, small fractionated doses of from 200 to 300 r are preferable with the treatment protracted over a considerably longer time The tumor dose may reach as high as 4000 or more roentgen units

SUPERVOLTAGE ROENTGEN THERAPY

In the treatment of deeply situated sarcomas e.g., in the pelvis, mediastinum, or retroperitoneal space, the million volt x-ray machine offers the important advantage of delivering the radiation dose to a much greater depth and into the center of the deeply situated tumor The skin erythema dose is quite high, so that a much larger dose may be given without skin damage when compared with the ordinary high voltage set up The million volt x ray apparatus has been a very satisfactory modality using a target skin distance of 70 cm a half value layer of 3 8 cm. of lead, treatment to each port of about 300 r daily and alternating through successive ports until a total dose of at least 3000 r × 2 or 3000 r × 4 has been administered

ROTATION ROENTGEN THERAPY OF DEEPLY SITUATED SARCOMAS

Although the idea of rotary irradiation is comparatively old, being mentioned by Kohl in 1906 and suggested by Pohl in 1913 it has been only during the recent postwar years that it has been developed on a scientific basis The principle of rotation radiation therapy is to rotate the patient about an axis through

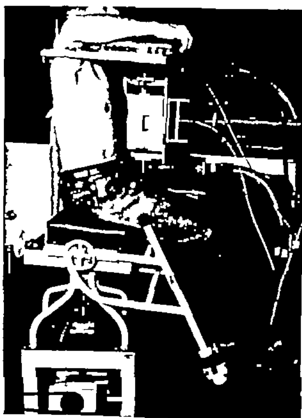


FIG. 76 Clinical photograph of a patient in position for rotation x ray therapy

TABLE 30 CONVERSION OF INOPERABLE TO OPERABLE SARCOMAS BY PRELIMINARY RADIATION THERAPY EXAMPLES*

Case	Sex	Age	Onset	Location	Description of Lesion	Reasons for Inoperability	Radiation Therapy	Operative Procedure	Pathology	End Result
J. H	Male	50	Feb 1945	Anterior chest Precardium	Thrice recurrent fungating tumor, 15 cm diameter Three ribs destroyed Precardium involved	Infiltration through chest wall, involvement of pericardium and pleura	High-voltage x-ray therapy 250 kv, 1 5 mm Cu, 50 cm , 300 r daily Total dose, 3000 r Gold radon seeds, 13 with 17 7 mc or 2351 mc -hrs	Radical cautery excision, using the actual cautery, 6-10-46	Undifferentiated rhabdomyosarcoma	1955, died of heart attack. No evidence recurrence Weight 250 pounds Pleura and pericardium exposed and epithelialized 10-year cure
R R	Female	25	May 1939	Left gluteal region	Bulky, adherent, ovoid mass, occupying entire buttock, 15 × 10 cm	Adherence and fixation	Four-gm radium pack, 15 cm distance, 8 gm -hrs daily for 19 consecutive days 152,000 mgh total dose 5-10-39 to 5-29-39	Radical surgical dissection of buttock Removal of gluteal muscles, 7-15-39	Rhabdomyosarcoma Grade III	Amenorrhea for one year Uterine myomectomy Two subsequent pregnancies with normal children July 1955, no evidence of recurrence. 16-year cure

Case	Sex	Age	Onset	Location	Description of Lesion	Reasons for Inoperability	Radiation Therapy	Operative Procedure	Pathology	End Result
H C	Male	34	Oct. 1930	Posterior cervical triangle	Twice recurrent, huge diffuse mass unencapsulated adherent to mastoid occiput, and spine	Recurrent infiltrating diffuse, adherent sarcoma	Four-gm. radium pack, 10 cm distance, 4 gm. hrs daily 100 000 mgh total dose Gold radon seeds, 11 totaling 16 mc 3-5-41 to 4-8-41	Radical surgical dissection including deep muscles, 5-22-41	Intermuscular liposarcoma	April 1955 no evidence of recurrence 16-year cure
F L.	Female	35	Feb 1930	Femoral trigone	Fungating fixed tumor 14 × 10 cm. Recurrent after incomplete surgery	Infiltration fixation extension above inguinal ligament	Four-gm radium pack, 25 cm distance 8 gm hrs. daily 252 000 mgh total dose. 10-23-36 to 12 10-36	Radical surgical dissection 1-8-37 Excision of femoral vein Skin graft. Later Kondoléon	Liposarcoma. Adult-cell type	Sept. 1955 living and well No evidence of recurrence 19-year cure

From Pack, and Miller Radiology 57 529 1951

the tumor at right angles to the x-ray beam or, vice versa, to rotate the x-ray tube around the stationary patient. Deeply situated sarcomas of inoperable status which are located in the mediastinum, pelvis, and retroperitoneal spaces are especially suitable for rotation x-ray therapy because of their central position in the longitudinal axis of the body. The patient is placed on a motor-driven rotating stool which is turned at a uniform rate, that is, one complete turn in 10 to 30 minutes, depending on the plan of the therapist. The distance from the x-ray target to the focusing diaphragm is 20 cm, and the distance from the focus to the axis of rotation, that is, the deeply situated sarcoma, is an additional 50 cm. or a total of 70 cm target-tumor distance The size of the skin portals is proportionate to the dimensions of the sarcoma A current of 6 ma and a potential of 180–200 kv are commonly used The filtration varies from a half-value layer (H V L) of 0 32 mm Cu to a H V L of 0 9 mm Cu By this rotation method a circular band of skin around the body is irradiated and tanned Jens Nielsen of Copenhagen, Denmark, who has been a leader in this method of x-ray therapy for esophageal cancer, considers this method similar to the employment of many small fields, "which are irradiated in succession, each with a fraction (from a fifteenth to a twentieth) of the full dose" The result of this method of x-ray therapy is that the skin and normal thoracic or abdominal organs receive a relatively small amount of radiation, while, conversely, the deeply situated sarcoma receives an enormous dose because of the constant centering of the beam where it should be This method takes full advantage of the differential sensitivities of normal and cancerous tissues to radiation therapy and fulfills as far as possible the primary requirement of successful irradiation, namely, to spare the normal tissues while destroying the cancer Nielsen in treating esophageal cancers by this method found the most suitable daily dosage to be a tumor dose of 150 to 200 r given in two daily sittings. The total dose approaching 5000 r into the substance of the tumor is consummated in the course of five to six weeks The bodily effect of these treatments is only a mild degree of radiation sickness characterized by slight nausea, anorexia, leukopenia, fatigue, lowered blood pressure, and loss of weight.

Preoperative Radiation Therapy

Although we deplore the use of irradiation as the sole treatment of soft part sarcomas which are operable, we admit that preoperative radiation treatment has occasional advantages It should be a selective rather than a routine procedure, however. If the neoplasm is situated on an extremity, and amputation is contemplated, x-ray treatment would be superfluous and unnecessary. Preoperative irradiation in certain circumstances can convert a technically inoperable sarcoma into one that is resectable and curable. Preoperative irradiation has also enabled us to substitute a radical dissection of the sarcoma for an amputation of an extremity, with preservation of the patient's life and limb. Sarcomas situated in the abdominal wall, thoracic cage, buttocks, groin, and deep paravertebral regions have regressed sufficiently following preliminary x-ray to make possible a curative radical local removal. As reviewed in the discussion on radiosensitivity, the majority of soft part sarcomas are relatively radioresistant Nevertheless, daily, protracted fractionated x-ray therapy can take advantage of the differential sensitivity of sarcoma and superjacent tissues and cause retardation of continued growth, shrinkage in the bulk of the tumor by 30 to 90 per cent, temporary inactivation, and incarceration of the tumor by productive fibrosis The cellular components of the sarcoma are partly destroyed and greatly sickened, mitoses are lessened, the blood vessels are par-

tially obliterated by endarteritic changes, and various degenerative processes may develop within the tumor substance The optimal time for later surgical excision is four to six weeks after completion of the irradiation This interval allows the vascular radiation reaction to subs[ide] and the full destructive effect of the radiation to be obtained

ACCOMPLISHMENTS OF RADIATION THERAPY IN TREATING TUMORS OF THE SOFT SOMATIC TISSUES

Effect of Irradiation on Fibrosarcoma

There were six individuals in our series of patients with fibrosarcomas who underwent local excision of their fibrosarcomas elsewhere and received irradiation to the operative site by us Of these, five (83 per cent) survived five years without evidence of neoplasia. It is difficult to evaluate accurately the role of irradiation in effecting a cure of these patients One patient however had a fibrosarcoma, Grade III, of the left forearm, including the ulnar bone, which was diagnosed six weeks after birth The tumor was treated by high-voltage x ray therapy and Coley s toxin, and the patient was free of any evidence of sarcoma five years after treatment. The x ray therapy consisted of x rays generated at 250 kv with 30 ma. over ¼ mm. Cu filtration target skin distance 50 cm., 250 r per day to the right forearm posteriorly for a total of 2000 r in air followed by 250 r daily to the right forearm anteriorly for a total of 1500 r in air The calculated tumor dose was 3350 r The mass subsided, and roentgenograms of the previously involved bone showed a normal condition four years later When last seen, four years after treatment muscular atrophy of the extremity was present but no loss of strength was noted. As a rule radiation has little to offer in effecting a cure and should always be secondary to refusal of or a contraindication to surgical therapy

Sarcoma Botryoides

Radiation therapy in our experience has never been curative for this disease and is of doubtful value in effec[tive] palliation.

Synovial Sarcoma

Of 14 patients with synovial sarc[oma] who were treated by us exclusively by irradiation, 4 are 5-year cures (28.5 per cent) Of these, in 2 the x ray was given over the postoperative site following a local excision elsewhere, so no credit can be given to irradiation for the cure here In the other 2, however incomplete excisions were performed elsewhere, and biopsies here revealed the presence of sarcoma In one patient radiation therapy to the tumor resulted in atrophy to the digit, and two years after roentgen therapy the digits were amputated and no presence of tumor was noted. In another patient a recurrent mass following excision of a tumor of the upper thigh was discovered by biopsy to be a synovial sarcoma It was treated by x ray therapy which controlled the local neoplasm but a metastasis to the groin developed eight months later This metastasis was treated by interstitial radon seeds and the patient has remained well for more than thirteen years. Her history follows.

CASE REPORT NO 4

M H the patient a 41 year-old German female first noted a tumor on the lateral aspect of the right thigh and hip in August, 1935 The mass was painful and gradually enlarged and in September 1936 was locally excised. The patient was well until six weeks before presenting herself [at] the Memorial Hospital on July 26 193[7] (eight and one half months after local e[xcision]

the tumor at right angles to the x-ray beam or, vice versa, to rotate the x-ray tube around the stationary patient. Deeply situated sarcomas of inoperable status which are located in the mediastinum, pelvis, and retroperitoneal spaces are especially suitable for rotation x-ray therapy because of their central position in the longitudinal axis of the body. The patient is placed on a motor-driven rotating stool which is turned at a uniform rate, that is, one complete turn in 10 to 30 minutes, depending on the plan of the therapist The distance from the x-ray target to the focusing diaphragm is 20 cm, and the distance from the focus to the axis of rotation, that is, the deeply situated sarcoma, is an additional 50 cm or a total of 70 cm target-tumor distance. The size of the skin portals is proportionate to the dimensions of the sarcoma A current of 6 ma and a potential of 180–200 kv are commonly used The filtration varies from a half-value layer (H V L) of 0 32 mm Cu to a H V L of 0 9 mm Cu By this rotation method a circular band of skin around the body is irradiated and tanned Jens Nielsen of Copenhagen, Denmark, who has been a leader in this method of x-ray therapy for esophageal cancer, considers this method similar to the employment of many small fields, "which are irradiated in succession, each with a fraction (from a fifteenth to a twentieth) of the full dose" The result of this method of x-ray therapy is that the skin and normal thoracic or abdominal organs receive a relatively small amount of radiation, while, conversely, the deeply situated sarcoma receives an enormous dose because of the constant centering of the beam where it should be This method takes full advantage of the differential sensitivities of normal and cancerous tissues to radiation therapy and fulfills as far as possible the primary requirement of successful irradiation, namely, to spare the normal tissues while destroying the cancer Nielsen in treating esophageal cancers by this method found the most suitable daily dosage to be a tumor dose of 150 to 200 r given in two daily sittings The total dose approaching 5000 r into the substance of the tumor is consummated in the course of five to six weeks The bodily effect of these treatments is only a mild degree of radiation sickness characterized by slight nausea, anorexia, leukopenia, fatigue, lowered blood pressure, and loss of weight

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cision) Since she first noted the recurrence, it had assumed rather bulky proportions, measuring 12 × 12 × 6 cm, which was represented by a moundlike swelling over the right greater trochanter, extending over the anterior aspect of the right upper femur as far as the femoral trigone There was also a roughly circular, nodular mass in the right groin which measured 3 × 3 × 3 5 cm

Biopsy of the recurrent mass revealed spindle-cell sarcoma of synovial origin

The patient was given *deep x-ray therapy,* receiving 250 r alternating anterior lateral ports daily until 3500 r × 2 were given from August 23 to September 4, 1937, with the following factors 200 kv and ½ mm Cu, 50 cm target-skin distance, 30 ma, 13 × 13 port There was marked regression, and the lateral port was increased to 4500 r from September 13 to September 20 There was a severe reaction with apparently complete regression of the disease On October 4, 1937, a recurrence of the disease in the right groin was treated by 11 55 mc gold radon seeds inserted into the residual disease in the groin The patient continues well

These data demonstrate that irradiation may effect a cure of synovial sarcoma in certain instances and reveal that certain neoplasms, although radioresistant, may nevertheless be radiocurable. These observations do not make claim that radiation therapy is superior to proper surgical intervention but do reveal that radiation therapy can be decidedly helpful as an adjunct to surgery or, if surgery is contraindicated, as a means of attempting a cure

In Briggs's report of nine cases of synovial sarcoma, five patients were alive, four of whom were treated by local excision followed by x-ray therapy.

Liposarcoma

The radiosensitivity of liposarcomas is greater than their radiocurability. Of 12 liposarcomas treated exclusively by irradiation, only 2 (15 6 per cent) were cured In the earlier years of our experience with liposarcomas, preoperative radiation was freely employed Analysis





Fig. 77 Recurrent inoperable liposarcoma of the thigh Preoperative irradiation, radical surgical excision, Kondoleon repair of lymphedematous extremity Fourteen-year cure (*Left*) Appearance 4 months after resection of the liposarcoma (*Right*) Appearance 6 years later (Pack and Miller, Radiology 57 529, 1951)

of these cases show that in at least 50 per cent of the patients a definite regression of the tumor occurred, and in 15 per cent of the patients the liposarcomas underwent a complete clinical disappearance. However microscopic foci of residual sarcoma were found in a majority of surgical specimens when these had been removed. The patients with long survival all had received radiation therapy usually as an adjunct to surgery There are several instances in which a recurrent primary inoperable liposarcoma has been made technically resectable by preliminary irradiation It is believed that postoperative irradiation is indicated in every instance in which this type of tumor was recurrent Metastases usually respond well to irradiation

Rhabdomyosarcoma

Rhabdomyosarcomas are radioresistant Their hemorrhagic tendency and gelatinous nature indicate their degree of radiosensitivity Irradiation either pre- or postoperatively was used in 61 patients in a series It is difficult to evaluate the role of irradiation in our series, because it was used chiefly in combination with excision or amputation. There were 11 patients who received preoperative irradiation in the form of x ray or radium-element packs In 9 of these patients, there was definite local recurrence of the tumor and the surgically excised specimen showed viable tumor cells It is accordingly emphasized that there is no indication for preoperative irradiation in these patients Forty four patients received some type of postoperative irradiation 35 of them developed definite local recurrences following the completion of the irradiation. On the basis of these data, we conclude that this tumor is not radiosensitive and that irradiation cannot be depended upon to prevent local recurrences when it is given following inadequate local excision

Kaposi's Sarcoma

Kaposi's sarcoma is radiosensitive and irradiation is the therapeutic method to be employed for multiple lesions or when the disease is diffusely extensive The more vascular macules or nodules are far more radiosensitive than the older indurated plaques Therefore it is essential to educate the patient to the importance of detecting and treating this tumor in the early phases The early macules or nodules will completely regress with doses of unfiltered low voltage roentgen therapy in the range of 1000 r to 2000 r A similar response was obtained with a similar dose by using a radium-element plaque at 1 cm distance. Over a large superficial region unfiltered low voltage x ray is employed 100 kv 20–30 cm. target-skin distance, and an average of 400 r to 800 r to individual regions It is essential to outline each of the irradiated areas on an anatomic chart lest the pigmented spots be mistaken later for new macules and be irradiated again, with the hazard of late necrosis

High voltage x ray therapy is reserved for deep tumors which involve lymph nodes mediastinum lung, abdominal viscera, etc. In two patients with disease of the os calcis and tibia, the tumor regressed following 200 kv therapy Cross fire technic was used, utilizing two small ports 300 r per day at 30 cm target-skin distance and 2 cm Al filters for a total dose of 1500–1800 r High voltage therapy has only been fairly successful and of palliative value in the involvement of the parenchymal organs with Kaposi's disease Conservative doses of roentgentherapy are to be given if the sarcoma is extensive or if edema is present. Because of the defective circulation in patients bearing this disease, overtreatment may readily result in necrosis, infection, and gangrene For similar reasons interstitial irradiation and blanket irradiation with large portals are hazardous

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SECTION III



The Treatment of Specific Tumors



CHAPTER 15

The Treatment of Tumors of Fibrous-tissue Origin

THE DESMOPLASTIC DIATHESIS AND ITS RELATIONSHIP TO NEOPLASTIC PROLIFERATION

INTRODUCTION

THE living organism does not really exist in the external atmosphere but, as described by Claude Bernard, in a *milieu interieur* which is formed by structural units and the circulating fluid that surrounds all cellular elements The maintenance of an exact physical environment within the body cells is effected by the compartmental distribution of the available water and solids between the cells per se and the interstitial spaces This separation into two distinct compartments (intracellular and extracellular) represents an evolutionary development whereby the extracellular compartment absorbs the brunt of the massive influx of water and metabolites and maintains a constancy of the cellular structures which deviates very little during normal states The maintenance of this exact organization is dependent largely upon the ability of the cells to permit a selective influx of certain ions and to prevent the permeation of others Chloride and sodium are the principal electrolytes of the extracellular compartment under ordinary circumstances During disease, disruption may occur in this selective absorbing ability of the cellular membranes, permitting abnormal ingress of certain ions into the cell and abnormalities in the protrusion of certain intracellular elements into the extracellular compartment. This has been observed following surgery as the result of hormonal imbalance (the administration of desoxycorticosterone acetate) and in simians and humans suffering from malaria

The extracellular compartment has been described by some as a "space" between the cells filled with osmotic fluid. This concept is erroneous, for that portion of tissue termed the *extracellular space* is really a complex structure maintaining its specific chemical composition form, and function, responding to hormonal and other metabolic demands, and undergoing specific pathologic alterations

This review will attempt to define this extracellular compartment, describe briefly its anatomy and physiology and discuss certain diseases which are apparently specific to this system, in the hope that a clearer understanding of the pathogenesis and nosology of neoplasms arising from these structures may be achieved

THE NORMAL EXTRACELLULAR COMPARTMENT

When Claude Bernard described the *milieu interieur* (that portion of tissue between the cells), it was imagined that this tissue segment consisted of a free space holding free water The discovery by Duran-Reynals that certain testicular extracts enhance the transport of material through tissue has stimulated much research in an attempt better to understand this phenomenon It has been discovered that this portion of tissue does not contain free fluid normally and that there exists within it an amorphous ground substance, specific cells, and fibrous material The so-called extracellular compartment is truly an organ, participating actively in many body reactions, and functions as an autonomous unit It had formerly been considered a mediocre structure to which were relegated the mundane functions of support, transport, and lubrication This organ, placed between the circulation and enchyma, is affected by the actio both, it participates in the biochen processes of the parenchymal cells, evidence is gradually accumulating t dicate that cell function depends gre upon the state of the ground subst matrix which surrounds the cell. T one cannot fully understand the act of drugs, hormones, poisons, dis processes, etc, upon the cell until t actions upon the matrix are known

The reciprocal reactions of prod of parenchymal metabolism upon the tracellular compartment and of t participating in the metabolism of connective tissue upon the cells of parenchyma await elucidation A n concise knowledge of these reactions aid materially in the better understa ing of disease processes (including plasms)

ANATOMY OF THE EXTRACELLULAR COMPARTMENT

The extracellular compartment consists of connective tissue This is a complex structure consisting of cells which mobile with multipotential facul



Fig 78 Living fibroblast cell in tissue culture of embryo mouse skin Phase photomicrograph dark contrast (× 1500 N A 1 25) The formed elements in the nucleus are nucleoli, and those in the cytoplasm are dark spherical "fat" droplets and elongated filamentous mitochondria (*Courtesy*, Dr Robert C Mellors and Cancer Research *13* 101, 1953)

fibrous elements which include collagen, reticulin, and elastin, and an amorphous ground substance consisting of acid poly saccharides and proteins Osmotic fluid normally circulates within these structures apparently as a molecular layer intimately adherent to the connective-tissue fibrils.

The cells are predominantly fibroblasts derived from mesenchyme Primitive mesenchymal cells also exist in certain sites. The fibroblasts are believed to produce the fibrous structures which are multicomponent systems, with collagen one constituent. Collagen connective tissue of human corium is about 1000 Angstrom units wide and many microns in length. The fibrils are characteristically cross banded, the distance between bands averaging 640 A and are extremely evenly spaced, as viewed by the electron microscope. This is so characteristic that it practically "fingerprints" collagen.

The argyrophilic fibers (reticulin) of newborn rats have recently been shown to have the same intraperiod structure as adult collagen but are thinner and with age a greater number of the thicker fibrils present themselves.

The amorphous material interspersed between the solid fibrous elements consists of acid polysaccharides and protein. It is very loosely associated with the collagen fibrils and can be easily separated from it by washing In the infant the amorphous material is very abundant, but with age the fibrous structures predominate

Mesenchyme from which connective tissue is derived is composed of undifferentiated cells separated by amorphous intercellular substance with an occasional fibril present. This is represented in the umbilical cord where the intercellular substance is soft and jellylike and where may be seen an occasional tiny fibril, As the mesenchymal cells differentiate into fibroblasts, fibers sheathed by a somewhat modified amorphous substance first appear Some of these are bound together into bundles as collagen others become elastic fibers The reaction of developing fibroblasts to testicular extracts epitomizes the normal development of the fibroblasts

Bensley has described this reaction and her observation may be abstracted as follows Immediately after the injection of testicular extract the fibroblasts become vacuolated and swollen mast cells degenerate, and the collagen fibers separate The metachromasia of the group substance is lost After 24 hours there is an increase in the number of fibroblasts, fibrillar degeneration is evident, and an increase in metachromatic staining of the ground substance is noted. In about a week definite fiber formation occurs related to active fibroblastic activity with intense metachromasia The reaction of the cells to the extract represents a recapitulation of their normal developmental history with acceleration of maturation and suggests that, in development and aging as well as in repair there is a progressive series of changes with a shift from the amorphous to the fibrous elements of the intercellular substance. Such changes are probably factors of the aging process, fibrosis and other sclerotic alterations The tissues of the aged, despite their dehydrated appearance, contain as much or even more water than tissues of young individuals and the dried up appearance is due almost exclusively to changes in the structural units

The question of the exact source of the intercellular substance has been a provocative one Most investigators believe that the intercellular substance is formed by the fibroblasts The exact mechanism of its production is not known, but *in vitro* studies have demonstrated a reciprocal relationship between the ability of the fibroblasts to produce collagen and the alterations in the surrounding media (changes in pH temperature, etc.) which influence the ability of the fibroblasts to produce collagen Some investigators such as Nageotte believe that the

intercellular substance is not produced by the fibroblasts but, instead, is manufactured by the body fluids The observation of Wolbach and Howe, that ascorbic acid is essential for the formation of collagen fibers and that animals depleted of vitamin C do not produce the acid mucopolysaccharides, indicates further that collagen is produced by the cells probably on an enzymatic basis.

THE NATURE OF THE GROUND SUBSTANCE OF THE EXTRACELLULAR COMPARTMENT

Our knowledge of this difficult subject has been greatly broadened by the studies of Karl Meyer The ground substance of connective tissue consists of acid polysaccharides and protein Practically nothing is known of the protein component of ground substance except that there is a typical aromatic amino

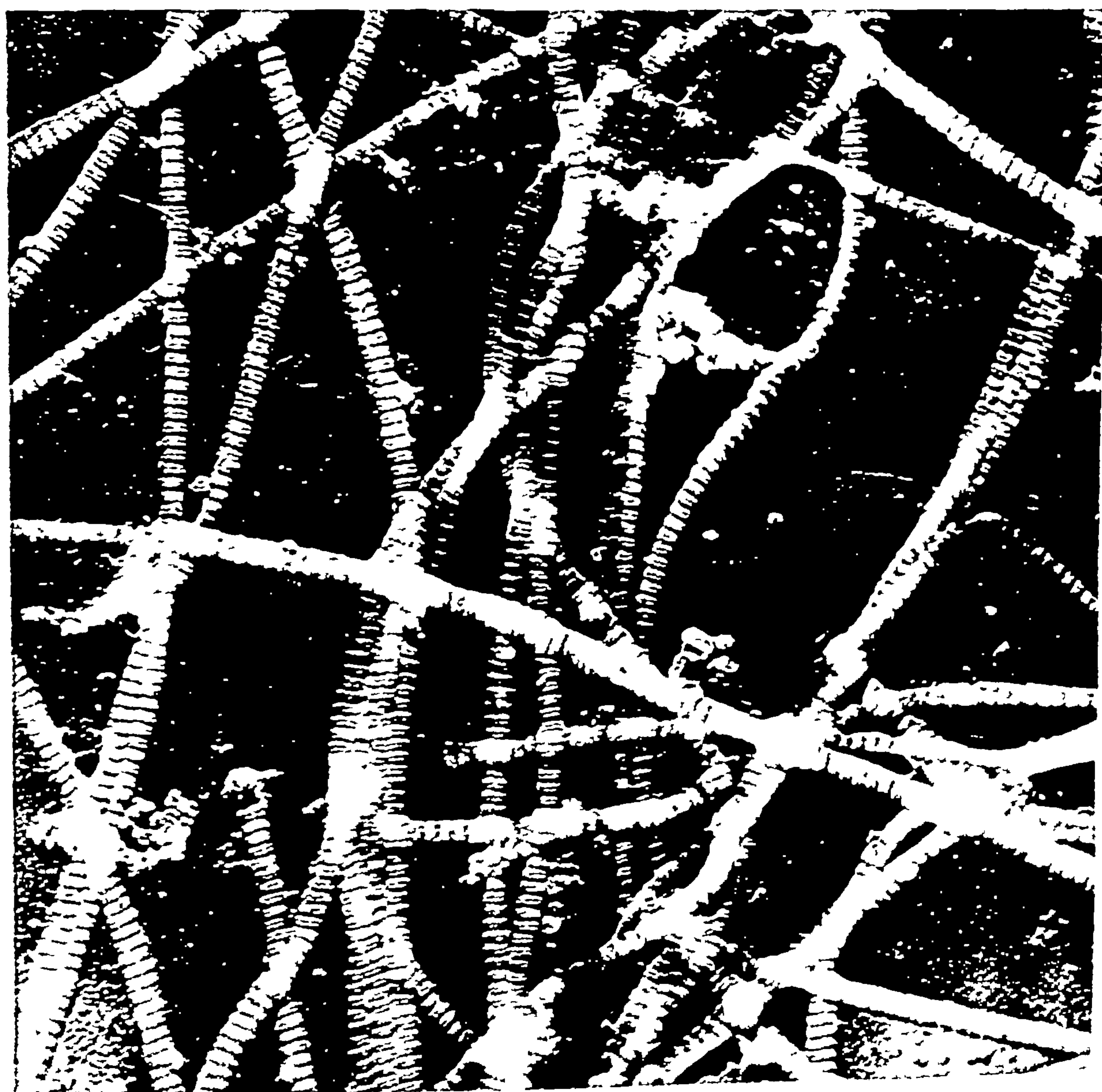


Fig 79 Collagen fibrils which have been thoroughly washed with distilled water The characteristic axial repeating period is evident, plus some intraperiod structure. There is little or no ground substance present (× 18,800) (*Courtesy*, Dr. Jerome Gross and Ann New York Acad Sc 52 964, 1950)

acid containing protein as revealed by ultraviolet absorption spectroscopic studies

The acid polysaccharides consist of hyaluronic acid, chondroitin sulfate and lesser known substances such as amyloid polysaccharide and capillary cement substance about which practically nothing is known. The hyaluronic acid appears to be present in greatest



FIG 80. This preparation was lightly washed to remove excessive ground substance. Most of the field except for the oval patch at the right is covered with a thin layer of amorphous substance A bundle of collagen fibrils on the right is seen imbedded in the matrix. (× 17 400) (*Courtesy* Dr Jerome Gross and Ann New York Acad. Sc. 52:964 1950)

amounts and has been extensively studied The methodology consists of (1) chemical studies of hyaluronate and the action of enzymes (hyaluronidase) upon it, (2) histochemical studies of their nature and locations by noting the metachromatic reaction of certain basic dyes (toluidine blue) when combined with acid mucopolysaccharides, and (3) the study of reactions following the administration of certain hormones, bacteria, toxins, etc

The Chemical Nature of Hyaluronic Acid

Hyaluronic acid is a high molecular polybasic acid which forms salts with proteins that precipitate in acid media The action of hyaluronic acid on protein resembles that of certain anionic detergents Hyaluronic acid, naturally, is polydispersible, *i e*, it has different molecular weights, but an average of 500,000 has been attributed to it Many of the observed chemical characteristics of naturally occurring hyaluronates would be due to the presence of acid anhydride linkages, both intermolecular and intramolecular The viscosity of naturally occurring hyaluronate solutions is high but drops rapidly when purified in neutral solutions The stabilizing effects on the acid anhydride linkages may be due to great amounts of polymerization which makes for the huge molecular size of naturally occurring hyaluronates (after Meyer) The main chemical linkage in hyaluronate is glucosidic, the basic unit is a disaccharide composed of acetylglucosamine and glucuronic acid The primary attack of hyaluronidase is on the glucosaminidic linkage, releasing the reducing group of the acetylglucosamine. It is present in varying amounts in all connective tissue including neoplasms Hyaluronic acid has been prepared from Rous's sarcoma in chickens about 1 gm. per kilo of tumor tissue was obtained, and the material had a nitrogen content of 3 8 per cent

The second mucopolysaccharide of connective tissue, chondroitin sulfate, is in an undegraded form, and its molecular weight has been estimated at 30,000 It is assumed to be similar but not identical to that of the cartilage The cartilage chondroitin sulfate is hydrolized by vesicular hyaluronidase but is not by pneumococcal hyaluronidase All tests have unequivocally demonstrated that the hydrolysis of chondroitin sulfate is considerably slower than that of hyaluronate The sulfate group is saponified by these enzymes The slow rate of hydrolysis of chondroitin sulfate undoubtedly is due to the more strongly polar character of the sulfate

The enzyme hyaluronidase has the ability of altering the physical state of the ground substance by acting on hyaluronates and thereby enhancing the spread of substances through the tissue spaces This enzyme is the active principal of the spreading factor of Duran-Reynals and is obtained by extraction from bulls' testes or from streptococci

HISTOCHEMICAL STUDIES OF THE GROUND SUBSTANCE OF THE EXTRACELLULAR COMPARTMENT

The method most frequently utilized to demonstrate acid mucopolysaccharides depends upon the metachromatic reaction given by certain basic dyes, such as toluidine blue, when combined with the acid mucopolysaccharides. The acid mucopolysaccharides in tissue known to contain sulfate as well as nonsulfate types will stain metachromatically. The strepococcal enzyme removes the metachromatic substance from various sites of nonsulfate-containing acid

mucopolysaccharides but fails to alter the sulfate-containing ones Testicular enzymes affect sulfate as well as the hyaluronates *in vitro* and prevent the metachromasia of both.

Acid mucopolysaccharides are abundant within cartilage nucleus pulposus and Wharton s jelly In cartilage the metachromatic matrix lies between dense meshes of collagenous fibers In Wharton s jelly the metachromatic substance fills the spaces between collagen fibrils almost completely There are no demonstrable collagenous fibers in nucleus pulposus but occasional reticular fibrils surround the groups of cells that lie within the metachromatic material. Cornea and vitreous humor owe their transparency to a high content of mucopolysaccharides It is possible that the mucopolysaccharides aid in the transport of materials for cell maintenance in these structures that do not have an intrinsic blood supply

The acid mucopolysaccharides are found within the secretions of epithelial structures as in the mucous glands of the respiratory gastrointestinal, and genitourinary tracts and it is believed that they function for protection and lubrication. Ovarian follicular fluid is strongly metachromatic in the human being, and it has been shown that testicular hyaluronidase disperses the columnar cells that surround ova at the time of fertilization.

Much metachromatic material is present in blood vessel walls Association of the metachromatic material with elastic fibers is common and suggests that it is performing the function of lubrication between layers that slide one on another The intima of the aorta contains mucopolysaccharides which possibly aid in its nutrition. The polysaccharides are diffusely scattered throughout the heart and are found in Aschoff bodies in recent scars within the myocardium and in acute rheumatic carditis

Within the connective tissues mucopolysaccharides are found in abundance and are noted in tendons ligaments, fasciae, and loose areolar tissues Small amounts are present in the normal derma of man and are most abundant in the papillary layer and around hair follicles The trachea, bronchii, the mammary gland and prostate also contain it.

It has been demonstrated in neoplasms especially in the actively growing mesenchymal tumors, in a human myxoma, and in a transplantable anaplastic methylcholanthrene-induced mouse tumor The Rous chicken sarcoma and a human mixed tumor of the salivary gland contain very large amounts of metachromatic substance Mucopolysaccharides are frequently conspicuous in the stroma of various epithelial neoplasms Wherever tried, testicular but not streptococcal, enzymes have removed the metachromatic substance of these sites

Newly formed granulation tissue is abundant in the metachromatic substance which becomes much less as the scar matures In scorbutus where the fibroblasts remain immature and the formation of collagen from reticulin is interfered with, the metachromatic substance persists after almost complete disappearance from the completely healed wound in a normal animal. The metachromatic substance of granulation tissue, removable by testes enzymes alone and hence resembling chondroitin sulfate may be related to the growth of the fibroblasts or to the actual formation of collagen as Meyer suggested in 1946

PHYSIOLOGY OF THE EXTRACELLULAR COMPARTMENT

The chemical and physical composition of the extracellular compartment can be altered by many factors When one recalls that this portion of the organism represents the internal environment of the cells it is not surprising that

many of the defense mechanisms aimed at preserving the viability of the cells occur within this extracellular compartment The tissues of this compartment participate actively in these reactions

1. The Effects of Infection

Certain diseases such as erysipelas, gangrene, pneumonia, and streptococcal infection can spread through the tissues with great rapidity It has been demonstrated that certain bacteria (streptococci) liberate the enzyme, hyaluronidase, which acts upon the hyaluronate, liquefying the media and permitting rapid ingress Thus, the ability of the infection to invade the tissues must be differentiated from the virulence of the infecting organisms The production of antibodies and other reactive phenomena occur and can be recognized as the response of tissue to the invading organisms which we recognize as inflammation, the formation of tubercles, gumma, etc., as well as such phenomena as the Arthus and Schwartzman reactions After subsequent introduction of a specific infecting organism, such complex reactions as sensitization, anaphylactic reactions, allergies, and certain little-understood chemical and structural alterations of adaptation occur

It should be noted that certain poisonous snakes and many insects also excrete the spreading factor, hyaluronidase, to assure the rapid invasion of the tissue by their venom Certain neoplasms also evoke reactions of the ground substance, and antihyaluronidase is found in experimental animals and humans bearing these cancers

2 The Effects of Hormones

Abundant evidence is available to indicate that different hormones of the organism exert marked influences upon the ground substance Estrogen decreases the permeability of the ground substance, while gonadotropic hormones increase its permeability Estrone greatly enhances the hydration of the tissues, but it has been demonstrated that this hormone also increases markedly the hyaluronic and chondroitin sulphuric acid It thus appears that the increased water within the tissues resulting from estrone administration is bound and not free water The increased spreading following the administration of gonadotropic hormones has been explained on the basis that the effect of the hormone is to render the ground substance water soluble, thus enhancing the rate of flow of substances traversing it

The adrenocortical extracts decrease the permeability, while adrenalectomy increases it Anterior pituitary hormones decrease spreading Cortisone does not exhibit any antihyaluronidase activity (Hechter), and it appears that desoxycorticosterone has no effect upon the viscosity of hyaluronic acid Intradermally administered epinephrine inhibits hyaluronidase spreading

Desoxycorticosterone also enhances the deposition of collagen and fibroblastic proliferation, the excretions of the sex glands (both testosterone and estradiol) inhibit these reactions Cortisone inhibits fibroplasia and thus wound healing, and ACTH inhibits anaphylactic and anaphylactoid reactions

The deposition of the ground substance (mucopolysaccharides) is also under hormonal control Thus, thyroidectomized animals treated with thyrotropic hormones develop exophthalmos, and the connective tissue of the orbits shows a marked increase in the metachromatic material

The sex skin of the monkey demonstrates a remarkable example of cyclic changes in the ground substance under hormonal control

3 Responses to Miscellaneous Substances

Certain drugs such as morphine and salicylic acid are said to decrease the

spreading induced by hyaluronidase. There are various inhibitors of hyaluronidase-spreading activity including epinephrine, morphine, antihistamines, salicylates and rutin. It is hypothesized that these inhibitors probably exert a beneficial effect for the host, for it has been shown that some of them prevent capillary damage due to toxic agents Thus salicylates prevent arteritis in certain allergic conditions and neutralize the toxic action of snake venom on capillaries Adrenocortical extracts prevent the action of leucotaxin and peptones to increase the permeability of skin capillaries (Hechter)

These observations indicate the myriad functions in which the extracellular compartment participates Bacteria, poisonous snakes and certain insects liberate hyaluronidase as a means of breaking down the barrier of the extracellular compartment to reach the body cells The ground substance (mucopolysaccharides) fibrous material, and fibroblasts participate vigorously in all reactions of repair (wound healing) transport defense, lubrication, and structural support.

As an organ of the body the units of the extracellular compartment are under hormonal control. It manifests reactions as the target organ to states of hormonal imbalance or abnormal chemical situations of the circulating fluids

The tissues of the extracellular compartment must have their necessary foods for maintenance and growth. Thus lack of vitamin C reduces ability of fibroblastic proliferation Pyridoxine deficiency causes a marked increase in the metachromatic substances of the arterial walls Nothing is known about the effects of protein deficiencies upon the protein moiety of the ground substance. Edema which not infrequently accompanies hypoproteinemia is known to retard wound healing in surgical patients

It is accordingly not surprising to observe this organ as the seat of disease processes (infectious metabolic, and neoplastic) The etiology and nature of these pathologic processes are little understood.

THE CONCEPT OF DISEASES OF COLLAGEN

Many disease processes manifest a fibrous-tissue component which accompanies or follows the actual pathologic entities Examples include scarring following inflammation, gumma, tuberculoma, and fibrosis which accompanies certain carcinomas.

In 1933 Klinge conceived that the connective tissue of the body could respond as an organ to a disease process He believed that in rheumatic fever and rheumatoid arthritis the connective tissue of the entire body was affected.

The brilliant studies of Klemperer served to classify such apparently diverse pathologic entities as rheumatic fever rheumatoid arthritis, polyarteritis acute lupus erythematosus, scleroderma, and dermatomyositis under the common generic heading of *diseases of the connective tissue* These diseases are characterized by qualitative and quantitative changes of the connective tissue, especially the extracellular components (fibrous structures and amorphous ground substance) The pathognomonic alterations consist of fibrinoid collagen damage *Fibrinoid changes* is a term applied to the collagen fibers which adopt the staining and structural qualities of fibrin which may represent an alteration of the fibers with either degeneration into or impregnation of fibrin. The exact nature is not known, but the abnormal fibers which are fibrinoid may be the result of abnormalities in their chemical composition. Klemperer's studies focused upon the extracellular compartment as an organ which could be diffusely diseased.

The etiology of these diseases is not known Fibrinoid changes can be pro-

duced by mere mechanical trauma, increase in arterial pressure, as well as by instances of hypersensitivity Certain authors have advanced the hypersensitivity factor as the main etiologic agent, but Klemperer presents evidence that other etiologic agents could produce these fibrinoid alterations He cautions against accepting the "allergic etiology" theory He does not deny the probable role of hypersensitivity but is fearful that acceptance of it as the sole basis would discourage adequate research into the true nature of these diseases

It is of interest that in the so-called diseases of collagen, an abnormality in the composition of the ground substance is present in addition to defects in the fibrous tissue Abnormalities in ground substance are present in scurvy as well as the alterations in the fibroblasts and collagen fibers. These findings suggest that a sufficient amount of normal ground substance must be available for the formation of normal fibrous tissue and that abnormal fibrous tissue may be due to abnormalities of ground substance from which the fibers are produced

Neither the exact chemical nature of the ground substance nor its exact site or method of production is completely understood Abnormalities in the ground substance could be produced by either dysfunction of the fibroblasts or abnormalities in the plasma, with the plasma contributing abnormal substances for the manufacture of the ground substance This latter is suggested in acute lupus erythematosus when there is an increase in the amorphous ground substance and possibly a qualitative abnormality also, there is an abnormal increase in the serum hexosamines. Treatment with ACTH decreases the serum hexosamines, and in one case so treated and reported by Klemperer, there was an associated decrease in the ground material. The fibers, however, appeared abnormal Significant changes in the serum proteins are present also in these diseases

Other provocative changes in lupus erythematosus are the presence of abnormal cells found in the serum and marrow, the so-called L E cells, and the hematoxylin bodies found in the tissues contain depolymerized desoxyribose nucleic acid The exact nature of derangements in nucleic acid metabolism of the mesenchymal cells in this disease is not manifest

The data have thus demonstrated that there is a group of diseases which appear to be metabolic in nature and which affect the connective-tissue organ The pathognomonic feature is abnormalities in the structural units of connective tissues, *viz*, abnormal amounts or types of ground substance, fibrous tissue, or increased fibroblastic activity The effects are generalized Similar but exaggerated and uncontrolled changes are observed in neoplasms and neoplasticlike proliferations of the interstitial compartment

DESMOPLASTIC DIATHESIS AND NEOPLASTIC FORMATION

The discussion thus far has demonstrated that the connective tissues (both *fibrous structures and the amorphous* ground substance) constitute an organ with specific anatomic, chemical, and physiologic characteristics They have a unique position in the structural arrangement of the body, being interspersed between the parenchymal cells of the different organs and the circulating fluids of the body. The various metabolic diseases which have been described as representing pathologic alterations of this organ invite research on such factors as the etiology, pathogenesis, alterations in chemical composition, and morbid anatomy, including cytochemistry, which will in time permit a

better understanding of the nature of the extracellular compartment and its disease processes

Such knowledge will undoubtedly contribute to a better understanding of the neoplasia involving the cells of this organ It is highly probable that changes in the medium can so influence the cells as to permit neoplastic changes Stewart has demonstrated that fibroblasts in tissue culture become malignant when 20-methylcholanthrene is added to the culture medium and that when these altered fibroblasts are injected into animals sarcoma, demonstrating all the manifestations of malignancy will develop at the site of the transplantation Nettleship has studied the sequence of events after the injection of 20-methylcholanthrene into hamsters Within 24 hours after injection, marked edema of the connective tissue develops and certain connective-tissue cells are found detached from the others and are swollen and granular These cells, altered within 24 hours after injection of the cancerogen, develop into frank sarcoma in a smooth gradual manner during a brief period. The altered cells proliferate and are present in groups and then large sheets of them are noted, and finally a sarcoma develops These animal experiments suggest the possibility that alterations in the fluid medium which bathes these cellular components of the fibrous tissue network may possibly play a role in inducing sarcomas in humans

When one recalls the great growth potentialities of the primitive mesenchyme and the fact that the various structures derived from it (reticuloendothelial system, hematopoietic system, and connective-tissue system including bone cartilage, muscle fat, synovial tissue, and fibrous tissue) are closely related to the primitive mesenchyme, it is not surprising that, under different stimuli, marked and protean manifestations of this growth capacity develop Furthermore, because of the ontogenetic relationship of these systems it surprising to find different comp of these systems participating in a disease process They even differe into one or another of the organs certain stimuli as in extramec hematopoiesis etc.

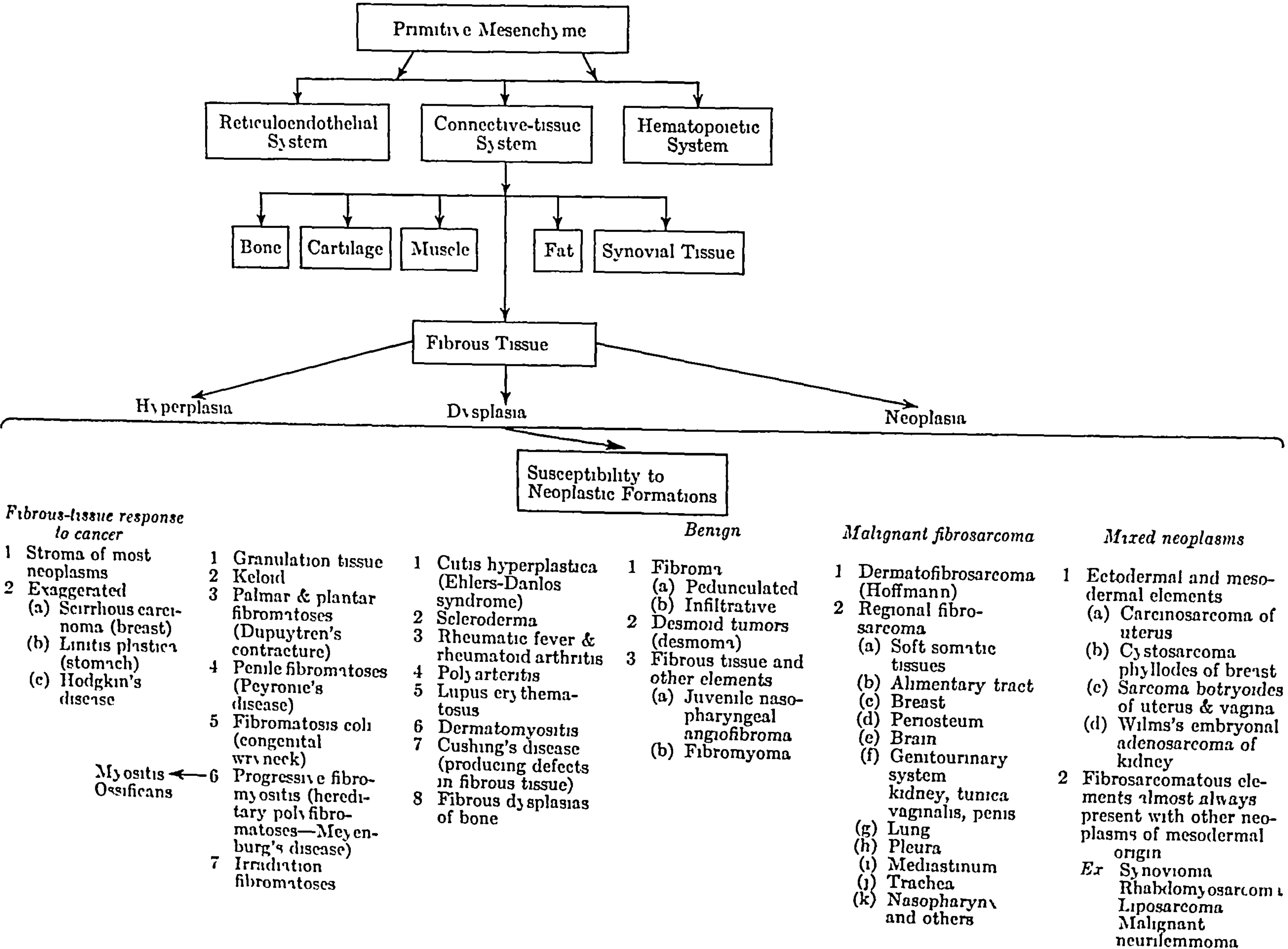
Alterations of the fibrous tissues which we are concerned in this sion) do occur in response to abr or noxious stimuli for example t duction of sarcoma by the inject 20-methylcholanthrene However nature of the alteration, as well degree and limitation are depe upon many factors including specie familial factors, and even indi variations For example since hor can markedly influence the conn tissue and its ground substanc status of hormonal balance of a giv dividual at the time, a stimulus e a fibrous tissue response, may ma alter the nature of the response examples follow

(1) *Specie alterations* If meth lanthrene is injected into guinea p per cent of the animals develop li comas, but if the same chemical jected into mice, none developes sarcoma.

(2) *Individual response to sti* If three patients receive burns o ilar depth and extent, one may de an extensive keloidal fibroma, ano simple hypertrophied scar and the a flat, supple cicatrix.

In discussing the various de ments of the fibrous tissue influ through the background of desmo diathesis, we have classified them three headings (Table 31) hyper dysplasia, and neoplasia The dysp which include such diseases as s derma, rheumatic fever rheum arthritis polyarteritis lupus erythe sus dermatomyositis and Cushing ease will not be discussed further i presentation for it is our intent m stress the relationship of *pathologic*

TABLE 31 THE NOSOLOGY OF DISEASES OF FIBROUS TISSUE



ations of fibrous tissue to neoplastic formation.

The interesting disease of *cutis hyperelastica* (Ehlers Danlos syndrome) represents a most intriguing entity of an abnormality of the fibrous tissue The three symptoms of this syndrome are pronounced hyperelasticity and hyperlaxity of the skin, hyperflexibility of the joints and marked fragility of the skin and its blood vessels The circus "rubber men" represent examples of this abnormality It usually begins in childhood and may be hereditary there is no known treatment. This entity represents an inborn error of mesenchymal metabolism Other structures of mesenchymal origin may be concomitantly deranged The patient may have von Recklinghausen's disease, lipomatosis etc. The Ehlers-Danlos syndrome might be considered the opposite of scleroderma, a condition in which the skin is bound intimately to the underlying structures and there is almost complete absence of elasticity The desmoplastic diathesis as evidenced here by a generalization of the process and frequent hereditary background, may be negative or positive in the nature of its manifestation

HYPERPLASIA

I Idiopathic Hyperplasia

The inherent capacity of the fibroblasts for reproduction after the slightest injury characteristically noted in granulation tissue, may result in a marked overgrowth (keloid formation) following a known stimulus a regional localization of idiopathic origin such as palmar fibromatosis (Dupuytren's contracture) plantar fibromatosis or penile fibromatosis (Peyronie's disease) or in fibromatosis coli (congenital wryneck) Each of these conditions represents localized fibrocytic overgrowth which is self limiting

Keloid (*cheloid*) is a renitent fibromatous neoplasticlike proliferation of the corium and subcutaneous tissue developing in especially susceptible dark skinned people, usually after trauma

Peyronie's disease represents a localized fibrosis of the penis which may extend into Buck's fascia and the tunica albuginea with the formation of plaques The same patient who has Peyronie's disease will not infrequently also suffer from Dupuytren's contracture and keloids, indicating that a diathesis probably exists

A *generalized systemic fibrositis* has been described. Creatinuria is common, and although the blood level of vitamin E is usually normal, the utilization curves indicate an abnormality in the metabolism of vitamin E Mixed natural tocopherols have been described as beneficial for the primary generalized, systemic fibrositis as well as for Peyronie's disease

Myositis ossificans has been described as a deposition of bone in muscles or about their insertions and as a low-grade inflammatory process characterized by the formation of bone within, or in contact with, muscle. The lesion involves primarily the fascial connective tissue, any muscular changes being secondary and degenerative Aberrant osteogenesis however is not limited to the skeletal system and voluntary muscles True bone formation has been reported as occurring in the meninges brain arteries lungs lymph nodes stomach, kidneys ureters bladder and skin, as well as in benign and malignant tumors

Myositis fibrosa progressiva (*Meyenburg's disease*) although it is a similar pathologic process, is distinctly and etiologically separate from the other types Rosenstirn noted a group of characteristic symptoms which sharply differentiated this condition as a clinical entity

Fibromatosis coli, or muscular torticollis, is an acquired or a congenital condition characterized by a fusiform swelling of the sternocleidomastoid muscle and occasionally other muscles in the neck such as the trapezius and those of the cervical group.

II. Response of Fibrous Tissue to Carcinoma

Carcinoma usually evokes a certain degree of fibrous-tissue proliferation (undoubtedly the host's reaction to the abnormal growth). Studies by Clark and Clark and by Warren on the mechanism whereby tumor transplants in rabbit's ear evoke a host's response yield interesting information. There is at first a rapid growth of endothelial cells toward the tumor from all directions. These cells form tubules which later become blood vessels and support the tumor growth. Immediately following, a hyperplasia of the fibrous-tissue elements in the tumor bed occurs and grows toward the tumor. It is an interesting conjecture why the blood vessels grow toward this unwanted new growth and support its development in the host, which growth is followed by an ingress of fibrous-tissue elements which apparently attempt to halt the growth. Embryonal tissue also stimulates blood vessel growth toward it but not the fibrous-tissue reaction. Other tissues do not stimulate either a blood vessel or fibrous-tissue proliferation and hence do not "take."

The reason why certain human cancers induce a profound fibroplastic reaction which surrounds and almost encapsulates the growing tumor is not known. This reaction of the tumor bed is quantitative and is inconspicuous in the average case. The exaggerated fibrous-tissue response in some instances resides perhaps not so much in the nature of the exciting agent as in personal or individual factors, *i.e.*, in patients with well-marked desmoplastic diathesis. Examples of this phenomenon are seen in scirrhus or fibrocarcinomas of the breast and in the cancerous type of linitis plastica. In the latter disease the diffuse fibrous hyperplasia is almost limited to the submucosa which is thick and inelastic, and it involves part or the whole of the organ, is covered by intact semiadherent mucosa, and is sharply delimited from the normal uninvolved segment of the stomach. The microscopic picture is that of overwhelming connective-tissue proliferation with the clusters of carcinoma cells so small and isolated as sometimes to require considerable diligence to discover and identify them. Yet this form of gastric cancer ultimately metastasizes even to bone. Compare the histologic structure and behavior of linitis plastica with the anaplastic carcinomas of the stomach, and compare scirrhous mammary cancers with the acute inflammatory carcinomas of the breast in which there is practically no host resistance. In response to neoplasm, these severe fibrous proliferations, which are not themselves neoplastic, probably represent vigorous but futile attempts of the host to protect itself against the expanding cancer. When more is understood about the tumor-tumor bed relationship and the mechanism of desmoplastic reaction to cancer, therapeutics may be evolved around such knowledge. It is believed by certain investigators that some of the beneficial effects of hormone therapy for prostatic and breast carcinoma depend upon the action of the hormones upon the fibrous tissue of the tumor bed.

Another example of the utilization of fibrous-tissue reaction in cancer therapeutics is *its reaction to radiation therapy.* Unpublished data of experiments utilizing Brown-Pearce rabbit epithelioma implanted in the testis serve to illustrate this point. When irradiated with low-voltage x-rays, a marked fibrosis about the tumor, with shrinkage of the neoplasm, was noted. If left unmolested, the tumor gradually disappeared leaving no trace on microscopic examination. Before complete disappearance,

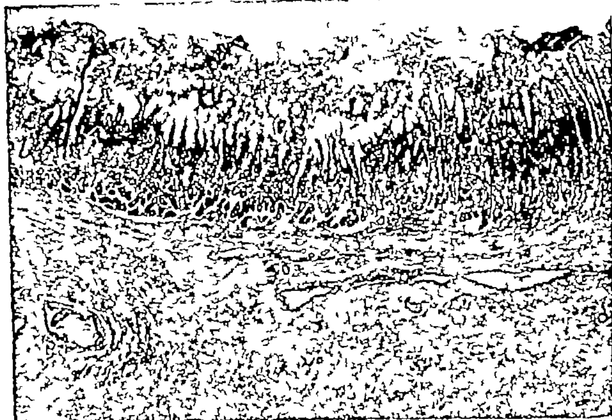


FIG 81. Photomicrograph of linitis plastica of the stomach (carcinoma type) demonstrating submucosal desmoplasia manifested by marked fibrosis and covered by intact semi adherent mucosa. Small nests of carcinoma cells are trapped within the overwhelming fibrous stroma.

if a tiny nubbin of residual tumor was transplanted into a fresh testicle it continued to grow after a brief latent period. These experiments indicate the manner in which the fibrous tissue reaction subsequent to irradiation may aid in the destruction of the neoplasms

III. THE FIBROUS TISSUE REACTION IN HODGKIN'S DISEASE

The exact nature of Hodgkin's disease per se has defied explanation. Whereas certain investigators believe that Hodgkin's disease is a neoplasm, with the eosinophils, Dorothy Reed cells, and fibrous tissue each contributing to the neoplastic growth, others believe that it represents an inflammatory granulomatous lesion. Tissue culture studies have aided in the study of the nature of Hodgkin's disease with its usual fibrosis. When the fibrous-tissue component of Hodgkin's disease is cultured *in vitro* thick collagen fibers are usually produced. When the cellular elements are transplanted in culture media, the lymphocytes reticulum cells and macrophages grow abundantly and from the coalition of these cells Dorothy Reed cells evolve Cytoplasmic inclusions have been identified in the Reed cells and at times in the fibroblasts Degradation of the cellular elements and liquefaction of the fibrin clot develop with aging of the culture medium Pure filtrates of Hodgkin tissue produce the same response when added to the culture medium of healthy human tissue These observations suggest that Hodgkin's granuloma may represent a body reaction to a pathogenic agent not yet identified and that the generalized fibrosis noted in this disease represents the response of fibrous tissue to the pathogen, similar to the localized fibrotic responses noted in gumma tuberculoma, and other localized granulomatous lesions The exaggerated fibroplasia in the older lesions was recognized by Thomas Hodgkin.

They occur most frequently in the soft somatic tissues.

MALIGNANT DEGENERATION OF BENIGN TUMORS

Several authors have traced the transition of fibrosarcomas from simple fibromas. However, it is impossible clinically to distinguish fibromas from slowly growing fibrosarcomas. The natural history of fibrosarcomas as revealed in an analysis of a rather large series indicates low-grade malignancy and insidiousness of growth before they produce symptoms of sufficient degree to cause the patient to seek medical attention. Unencapsulated fibromas of fascia, especially of the extremities, may be classified on excision as histologically benign but are prone to recur, to infiltrate, to extend centripetally toward the trunk, and to show increasing cellularity with successive recurrences.

MISCELLANEOUS

Fibrosarcomas have been described in a bone lesion of osteitis fibrosa cystica secondary to a parathyroid adenoma. No etiologic relationship was observed between the occurrence of the sarcoma and occupation, race, and nationality of the patient. No metabolic abnormalities were observed, and blood chemical findings when taken were normal in all instances.

We have reported the development of sarcoma in myositis ossificans and an unusual instance of fibrosarcoma occurring in myositis fibrosa progressiva (Meyenburg's hereditary polyfibromatosis) which caused death by pulmonary metastasis.

SUMMARY

An attempt has been made to develop the concept that the extracellular compartment exists as an organ of the body and as such has its specific anatomic, physiologic, and pathologic characteristics.

A number of metabolic disorders, which include rheumatic fever, rheumatoid arthritis, lupus erythematosus, polyarteritis nodosa, scleroderma, etc., are pathologic manifestations of the entire connective tissue of the body.

The theme has been developed that tumorlike proliferations of connective tissue such as keloid, palmar fibromatosis (Dupuytren's contracture), plantar fibromatosis, fibromatosis coli (congenital wryneck), Peyronie's disease, myositis fibrosa progressiva, and fibrous dysplasia of bone in all probability represent localized expressions of a generalized disorder of the connective-tissue system—a desmoplastic diathesis.

Carcinoma usually evokes a fibrous-tissue reaction which probably represents the host's response to the neoplasm. This fibroblastic reaction may be profoundly exaggerated, as in cases of scirrhous carcinoma of the breast, linitis plastica, etc. These severe fibrous proliferations in response to a neoplasm—and which are not themselves neoplastic—probably represent a vigorous but futile attempt of the host to protect itself against the expanding cancer.

Certain neoplasms of fibrous tissue such as recurring dermatofibroma of Darier, infiltrative fibromas, and dermatofibrosarcoma protuberans most likely represent localized manifestations of neoplastic degenerations of mesenchyme. Such concomitant abnormalities as lipomatosis, fibrolipomatosis, neurofibromatosis, etc., lend support to this belief.

Evidence is presented that certain neoplasms of connective tissue are under hormonal control. These include desmomas, juvenile nasopharyngeal angiofibromas, and mammary fibroadenomas.

We have attempted to develop the

concept that neoplasms of fibrous tissue do in certain instances, represent a diathesis of the connective-system organ as a whole, akin to the metabolic disease of collagen. Increased knowledge of the normal anatomic, chemical, and physiologic characteristics of this organ and of the "disease of collagen" will undoubtedly enhance our knowledge of the etiology pathogenesis nosology and methods of ablating neoplasms arising in this organ

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TUMORLIKE OR PRENEOPLASTIC FIBROUS GROWTHS

KELOID (CHELOID)—KELOIDAL FIBROMA

KELOID (cheloid), keloidal fibroma, is a fibromatous neoplasticlike proliferation of the corium and subcutaneous tissue It develops in susceptible dark-skinned people, usually after trauma The injury may be severe (*e g*, a burn) or so trifling that the keloid develops without the patient's being aware of any previous trauma. Mention has already been made of a tribal custom among certain Africans in which the skin is scarified in various patterns, later enhanced by the growth of keloids conforming to this design

It is difficult to estimate the true incidence of keloids, because they are so prevalent in certain geographic areas that no treatment is sought by the patient The exact etiology is not known, although the patient definitely bears a diathesis to the overgrowth of fibrous tissue This diathesis is congenital although not necessarily inherited

Keloid may occur in the skin of any location but is especially prone to develop on the ears and in the presternal and intermammary skin, particularly when this skin is unusually tense between closely approximated breasts

The bulk of the tumor consists of an overgrowth of hyaline, collagenous tissue with little cellularity Histogenetically, it is a fibroblastoma (Fig 84) The fact that the fibrinoid changes are noted histologically suggests chemical alterations of the ground substance as well as hypertrophy of the fibrous components Elastic fibers are absent, and blood vessels are usually scanty The epidermis is smooth, atrophic, and attenuated The color is red or violaceous at the time of its florid growth, but later it fades to pink or white as the tumor ages. Keloids seldom if ever become necrotic and ulcerated.

This lesion is endowed with surprising growth capacity Perhaps this propensity is the distinction between it and the hypertrophic scar The latter is confined to the extent of the original injury, whereas the keloid propagates in irregular, knobby, lobulated outgrowths well beyond the site of trauma. The projection of growth is indeterminate, but always it is circumscribed Rapid growth may continue for weeks or months after which growth momentum is lost and the keloid will remain stationary in size The term

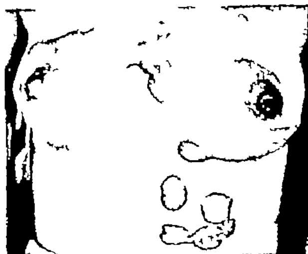
keloidal fibroma better defines this over growth and might be especially useful to describe the larger overgrowth In our experience these tumors have remained benign, metastases have not occurred. One patient developed an independent malignant neurilemmoma beneath a keloidal fibroma sequential to a burn Horton Crawford and Oakey report the development of a carcinoma in a keloid on the face of a 30-year-old female and cite one other instance of such occur rence reported in the literature

The subjective symptoms of the keloid are sometimes more annoying to the pa tient than the cosmetic blemish Pain itching, paresthesias and increased epi critic sensibility are common accompani ments The intensity of the subjective symptoms are independent of the size of the overgrowth

TREATMENT OF KELOIDAL FIBROMA

Spontaneous involution of the tumor occasionally occurs, with blanching and flattening of the convoluted folds We have attempted the interstitial use of various reputed fibrolytic substances without discernible benefit. The results of surgical excision have been disappointing because of the rapidity and ex tent of local recurrence of the tumor Even a suture puncture furnishes a nidus for the origin of a new keloid Absorbable sutures such as catgut have been discarded and supplanted by the less ir ritating silk or cotton Endotherm ex cision, in particular has been followed by recurrent keloidal growth If excision and wound closure are attempted, the defect should be approximated without tension Overcorrection of the wound with careful approximation of the skin edges may diminish the amount of fibrous tissue which may grow into the approximated skin The surgeon may not appreciate how widely the tumor ex tends beyond its palpable margins

Prophylactic postoperative radiation



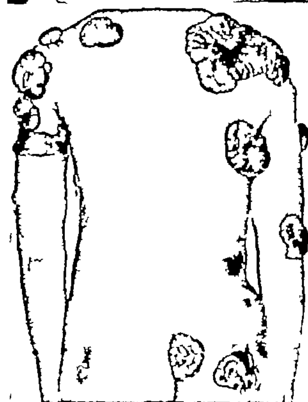


FIG 82 (*Upper*) Multiple keloids developing in a Chinese girl following either occult or overt trauma. (*Lower*) Multiple keloids devel oping in a Negress.

therapy is attended by variable and un predictable success but it is nevertheless worth while Short-distance, low voltage x ray treatment is given, or a radium plaque is applied in about 10 to 14 days after the operation, our rule has been to give this treatment on the day following removal of the sutures We do not give preoperative irradiation Irradiation as the sole treatment may slowly blanch and flatten the tumor and relieve the distressing itching and burning. Usually only from 200 to 250 r are given at



FIG 83 A Keloidal fibroma which developed in a burn scar of a dark-skinned individual The fibrous overgrowth propagates as lobulated outgrowths beyond the site of trauma B Result following low-voltage roentgen therapy

weekly intervals for three or four doses This form of treatment is probably preferred for keloids which cover large surfaces as those following burns (Fig 83) It would, however, be preferable to excise surgically the damaged tissue In such instances it is preferable to excise a segment of the defect and suture the opposing edges By staging such segmental excision a large region may be excised without resorting to skin-grafting It must be borne in mind that if skin-grafting is a contemplated procedure, the donors site becomes a focus for new keloid formation Pinch graft sites are particularly prone to develop keloids



FIG 84 Photomicrograph of keloidal fibroma of patient shown in Fig 83 Note the overgrowth of hyaline collagenous tissue, fibrinoid alterations, scarcity of cells, and the atrophic, attenuated epidermis

Localized cryotherapy with carbon dioxide ice is occasionally successful Attempts at altering the growth characteristics of keloids by the use of ACTH and cortisone are being experimented with, but to date clinical results have been disappointing

The following case report demonstrates the natural history of a keloid formation and a method of treatment which was successful in this patient

CASE REPORT NO. 5 KELOIDAL FIBROMA TREATED BY RADIATION THERAPY

R B, a 40-year-old man, in June, 1935 sustained a severe burn involving the left arm, left thigh, and posterior chest following explosion of an alcohol lamp He was

treated by tannic acid applications, and an attempt at application of discrete pinch grafts was unsuccessful. Three months later the scar showed signs of hypertrophy and the patient experienced various paresthesias including severe pain.

On examination, April 9 1936 there was an extensive keloid involving the entire left arm particularly the medial aspect with contracture of the elbow A very thick, renitent, inflexible keloidal formation involved the entire posterior chest wall. On the left side extending across the midline to the midscapular region, the keloid was elevated and rigid. The left arm had greatly impaired function. Biopsy revealed keloidal fibroma (Figs 83A and 84)

Treatment

Low voltage x ray therapy was administered utilizing the following factors 100 kv 2 mm of aluminum filter 30 cm target skin distance, 5 ma. current, 200 r using fairly large ports and rotating until a total dose of 800 r was given to each of the various fields The contracture in the cubitus was corrected by surgical excision and transplantation of a pedicled tube flap

End Results

Complete restoration of function of the arm resulted. The thick keloid completely regressed, with a soft, thin supple scar no thicker in texture than normal skin (Fig 83B)

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PALMAR FIBROMATOSIS (DUPUYTREN'S CONTRACTURE)

Dupuytren in 1832 described the palmar deformity which bears his name It is reported that the permanent flexion deformity of the fingers occurring in aged individuals described by Plater in 1614 is the defect known today as Dupuytren's contracture Skoog in 1948 called attention to the frequent coexistence of plantar fibromatosis with Dupuytren's contracture and indicated that the defect probably represents a desmoplastic diathesis

Dupuytren's contracture consists of a flexion contraction of a portion of the *superficial* palmar aponeurosis which is due usually to a fibrous replacement of the normal aponeurotic tissues, producing a localized nodular enlargement either in the palm or in fingers with a resultant deformity either

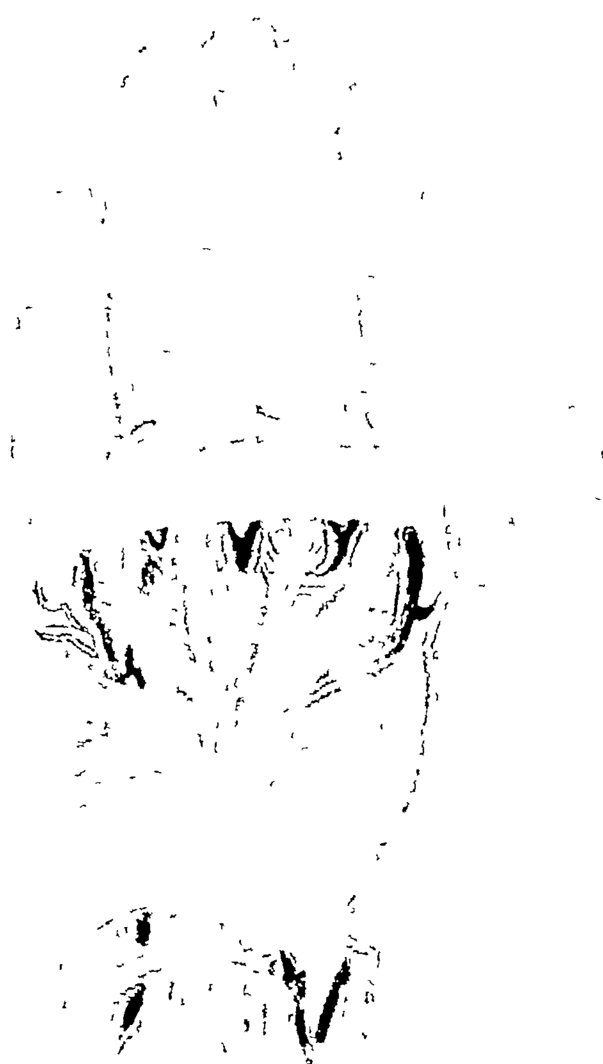


FIG. 85. Anatomic dissection demonstrating the palmar aponeurosis. Note how the fascial bands extend to the fingers and how contractures of these bands would produce corresponding contractures of the digits. (*After* Grant.)

of the palm or one of the involved fingers.

ANATOMY OF THE PALMAR APONEUROSIS

The palmar aponeurosis is the superficial palmar fascia which usually arises as a prolongation of the palmaris longus muscle (reputed to be absent in 12.5 per cent of humans—Kalberg). From its origin the fascia flares out to cover most of the middle portion of the palm as a solid sheath, after which it divides into four equal parts, inserting into each of the four fingers. Occasionally a fifth division inserts into the thumb. The fascia is attached to the skin by a specialized fatty tissue connecting the superficial fibers of the fascia to the skin. It is involvement of the superficial fibers during the disease which produces slight dermal invaginations which, associated with atrophy of the fatty tissue, result in a hidebound aspect of the overlying skin. The blood supply is poor, and innervation, consisting of end organs, is only occasionally present. The function of the palmar aponeurosis has invited great speculation, but it is said to aid significantly in maintaining a good grip of the hand, preventing the overlying skin from slipping, and keeping the flexor tendons in position.



Fig. 89 Anatomic dissection illustrating the deeper structures of the hand after removal of the palmar aponeurosis. For complete cure of fibrosis of the aponeurosis, it is necessary to remove the aponeurosis in its entirety

CLINICAL FEATURES OF DUPUYTREN'S CONTRACTURE

Incidence

This disorder occurs in from 1 to 2 per cent of all people (Bunnell) This figure fits in well when different groups are analyzed. Thus Schnitzler reported 1 7 per cent of 80 000 out patients in a hospital in Munich, and Anderson reported 1.3 per cent of 2600 adult patients

Sex

Males are affected much more frequently than females, and in a series of 1725 patients (Skoog) 15 per cent were women and 85 per cent were men. A similar situation prevails when families who suffer this defect as an hereditary abnormality are analyzed for sexual distribution of the disorder Of 118 such patients 103 were males and 15 were females

Age

The disease is most frequent in middle-aged adults A breakdown of the ages of 666 individuals revealed that 21 were from 0 to 19 years old 57 from 20 to 29 years, 114 between 30 and 39 years 119 between 40 and 49 years, 166 between 50 and 59 years, 141 between 60





Fig 87 (*Upper*) Clinical photograph of an early lesion of palmar fibromatosis in a 45-year-old female Note the small nodules in the distal palmar crease, proximal to the ring finger Minimal contracture of this finger was evident to the examining physician although the patient was not aware of the beginning contracture (*Lower*) More advanced stage of Dupuytren's contracture

and 69 years, 41 between 70 and 79 years, and 3 were between 80 and 89 years old This increased incidence with increase in age is of importance and suggests that an etiologic factor may be either constant trauma or related changes of the corium due to the aging process. Of 1,000,000 examinees for induction into the United States Army who were between 20 and 35 years of age, 5 were rejected because of palmar fibromatosis.

Location

Involvement is often bilateral Reported series, however, indicate that the right hand is the involved member in about 70 per cent of patients The reason for this discrepancy may be due to the fact that most people are right-handed and will present themselves for treatment when the defect produces functional disability In addition, a period of from 10 to 15 years may elapse from the onset of the disorder in one hand before the opposite palm becomes involved The ring finger is the one most frequently involved Analysis of a large number of reported cases revealed the following distribution of involvement the palm alone, 2365 instances, thumb, 79 instances, index finger, 135, middle finger, 570, ring finger, 1550, little finger, 1299 (Conway)

Race

The disease is almost exclusively limited to the white race We are not familiar with any reports of Negroes or Asiatics suffering from Dupuytren's contracture This is of interest in view of the propensity of Negroes to develop keloids.

Symptoms

The presenting symptom is a nodular subcutaneous enlargement, either in the palm or in one of the fingers It tends to increase in size and gradually to become more tender The development of a flexion deformity may be so gradual and insidious as to escape detection until it has progressed to a moderate degree The patient generally seeks treatment because of difficulty in shaking hands, washing, etc A delay of from 1 to 15 years generally exists until the patient

seeks therapy for this disorder The differential diagnosis includes the congenital flexion deformity, flexion contracture secondary to tendovaginitis polyarthritis etc. and occupational flexion contractures seen in tailors writers editors etc.

ETIOLOGY OF DUPUYTREN S CONTRACTURE

TRAUMA

Dupuytren believed that the disease that bears his name was due to constant trauma to the palm and fingers Others have also ascribed a traumatic origin to this defect, which is most frequently though by no means always, found in individuals who perform heavy to medium manual labor (Chap 4, The Role of Trauma in Inducing Sarcomas)

HEREDITY

That this disorder is an inherited abnormality in certain instances is borne out by the fact that 118 individuals from families afflicted with it have been reported Many authors have presented instances of the disease among siblings or offspring Whether the transmission is a dominant or a recessive characteristic is not known.

ASSOCIATION OF PALMAR FIBROMATOSIS WITH OTHER COLLAGEN DISEASES

Dupuytren s contracture has been reported as occurring not infrequently in association with other collagen diseases It has been observed in conjunction with Peyronie s disease (of 549 reported cases of Peyronie s disease, 22 suffered an associated Dupuytren s contracture) and plantar fibromatosis was present in a number of instances It has also been described in association with rheumatism gout and arthritis

Other accused etiologic factors include various neuropathies (peripheral nerve lesions, spinal cord lesions cerebral lesions sympathetic nerve lesions neurosyphilis) certain endocrine disturbances (including diabetes and thyroid, parathyroid, and pituitary deficiencies) abnormalities in development, local infection, tuberculosis chronic intoxication contraction of the palmaris longus muscle, etc.

It must be stated that 125 years after this disorder was described by Dupuytren its etiology remains enigmatic.

PATHOLOGY OF DUPUYTREN S CONTRACTURE

Two extensive investigations pertaining to the pathology and pathogenesis of this disorder have been conducted, one by Meyerding and his group at the Mayo Clinic and another by Skoog who studied the material at the Queen Victoria Hospital in England and at the University of Upsala Sweden Meyerding believes that the disorder begins as a localized growth of fibroblasts which contains many mitoses and grows in a nodular manner After the phase of cellular activity subsides fibrous-tissue sheaths are formed, and the region becomes more and more acellular The usual contraction of the fibrous sheaths results in the contracture deformity usually associated



FIG. 88. Photomicrograph of palmar fibromatosis during the active fibroblastic stage (× 150)

with Dupuytren's contracture. Although the defect begins as a localized fibroblastic overgrowth, it gradually spreads to involve the entire aponeurosis, and it infiltrates the subcutaneous fat and the skin. Meyerding observed that the degree of the contracture is related to the duration of the disease. He does not consider it a neoplastic proliferation but rather a manifestation of a chronic inflammatory process. He believes it best to remove the defect surgically after it has attained the state of acellularity.

Skoog, who performed extensive examinations of variously stained specimens which included electron microscopic examination of diseased tissues, believes the disease process is related to overstretching or rupture of the fibers of the palmar aponeurosis. Hypertrophic scarification occurs at these sites with subsequent shrinkage of the scarified regions. This enhances the avascularity of the tissue, increasing its susceptibility to further damage.

The deeper structures are infrequently involved.

Horwitz in 1942 examined 35 patients with Dupuytren's contracture and called attention to the close association between the pathology of this disorder and such fibroplasias as keloids and desmomas. He called it a *benign fibroplasia of the palmar connective tissue.* Clay in 1944 described a similar pathologic change but considered it neoplastic, terming it a *cellular fibroma of the palmar fascia.* His designation of the neoplastic nature of this overgrowth is not generally accepted.

TREATMENT OF DUPUYTREN'S CONTRACTURE

The only satisfactory form of therapy is excision of the involved fascia. The pendulum of surgical technics has swung from the earliest practice of Cooper and Adams, who simply divided the fibrous bands through small incisions, to attempts at completely removing the palmar fascia (Iverson, Bunnell, Skoog, etc.). The Kocher operation which consists of a more limited total extirpation advocated in 1887, is again being popularized by certain surgeons, including Conway, because of the complications which may ensue subsequent to attempts at complete extirpation of the palmar fascia. The exposure to the palmar aponeurosis depends upon the location and extent of the disease process. Toward the end of the last century, tiny excisions were made over the most severe portion of the disorder, and fibers were merely transected. During the early part of this century, extensive incisions were made over the palm for complete fasciectomy. This is evidenced by the incision advocated by Iverson in 1909, which extended from the thenar eminence to the carpal ligament and thence to the thumb. Every conceivable combination of incisions to permit access to the underlying tissues has been described. The very number of the proponents for each demonstrates both the complexity of the problem and the fact that each incision has value for certain situations. Many of the incisions have attempted to follow the crease lines of the hand, but Conway has clearly indicated that any horizontal incision, regardless of its relationship to the normal palmar creases, will heal well, with good functional results, providing all surgical disciplines are maintained.

The authors favor the incision described by McIndoe with modifications depending upon existing circumstances (Fig. 89). After a careful preoperative preparation of the entire arm, which is carefully cleansed with an antiseptic solution such as pHisoHex, Metaphen or other suitable solution, the arm is wrapped in sterile dressings. Under general anesthesia an Esmarch bandage is applied and a tourniquet is placed over the elbow. The incisions are made over the palm and the fingers as indicated, thick skin flaps with attached fat

are developed gentle retraction with skin hooks is maintained, and the dissection of the palmar aponeurosis is begun proximally and extended distally The incisions in the fingers permit access to the aponeurotic extensions which are severed and by subcutaneous dissection are joined to the main mobilized aponeurosis The number of fingers to be incised depends upon the extent of the involvement Care must be taken to avoid damage to the underlying vessels and nerves After the aponeurosectomy has been completed, the tourniquet is released, and complete hemostasis must be assured. A postoperative hematoma can be responsible for a crippled hand. The wound is closed with fine silk sutures and bandaged with a large bolus pressure dressing in a position of slight flexion.

Conway has emphasized that postoperative slough of the skin is due essentially to involvement of the skin by the disease process and whenever the skin is found thin and infiltrated by the fibrous tissue during the operation, the wisest procedure is to excise *in toto* the damaged skin and repair the defect with a thick split thickness skin graft or a full thickness skin graft. Stitches are left in for about two weeks Complete splinting during the postoperative care is not necessary and a careful balance between rest and activity should be adopted. Good physiotherapy can sometimes exert a beneficial postoperative effect.

In a series of 307 patients reported by various authors, the results after complete aponeurosectomy were reported as excellent in 73 per cent of the cases and poor in 10 per cent.

Other procedures, in addition to operative removal, have been advocated Irradiation by x ray or radium has been recommended, and it would appear that this procedure might be indicated in arresting further progress in the very early lesions Small doses of low voltage



Fig 89 Incision for excising palmar fibromatosis. The horizontal palmar incision permits access to the palmar aponeurosis. The S and J finger incisions permit exposure for resecting the digital fibrous bands where indicated. Subdermal tunneling dissection permits en bloc excision of the diseased aponeurosis. The number extent, and types of incisions depend upon individual situations.

x ray might be indicated in certain early instances In the late stages when fibrous tissue replacement has occurred, irradiation is of no avail.

Vitamin E and ACTH or cortisone have been advocated, but reports of their use have been discouraging Other therapeutic measures such as local injection of chemicals reputed to have a fibrolysin ability electrical stimulation, or iontophoresis and other empiric measures which have been suggested are mentioned here only to be condemned

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PLANTAR FIBROMATOSIS

When feet are amputated for a benign condition because of a mistaken diagnosis of a malignant neoplasm, it becomes essential to emphasize the differential diagnosis between the two situations This has occurred when fibromatosis of the plantar fascia was mistaken for a fibrosarcoma, with the calamitous aftermath of an amputation This discussion will present those features which characterize the pathologic and clinical nature of plantar fibromatosis

Plantar fibromatosis is the fibrous replacement of the plantar aponeurosis, similar pathologically to palmar fibromatosis (Dupuytren's contracture) In fact, when Dupuytren first described the condition which bears his name, he also made mention of the same situation as an affliction of the plantar fascia

INCIDENCE

The rarity of plantar fibromatosis is indicated by the fact that there have been only 120 cases reported in the literature However it must occur more frequently but many cases are not reported The high incidence of Dupuytren's contracture coexistent with plantar fibromatosis would suggest a higher incidence for the latter than the literature would indicate. Pickren, Smith Stevenson, and Stout record 7 cases operated upon at Presbyterian Hospital (New York) during a 22 year period, making an incidence of 1 75 per 100 000 admissions. It is of interest in this regard that 2 of the patients reported from the Presbyterian Hospital series suffered amputation of a foot, one because of recurrences of the fibromatosis and the other because of a misdiagnosis of fibrosarcoma. The latter patient, a 36-year-old male 3 years after the amputation developed nodules of his palmar fascia and a similar nodule of the sole of his opposite foot.

ETIOLOGY

The etiology is unknown The factor of trauma is suggested in some cases but the number of injuries that are unassociated with plantar fibromatosis and the fact that this disorder can occur

without trauma would indicate that trauma, if a factor, would be associated with some other etiologic agent Certain authors (Ledderhose, Skoog) believe that weight-bearing following a period of immobilization (such as that incident to the treatment of a fracture) by causing rupture of the fascial fibers plays a basic etiologic role in the production of plantar fibromatosis

The disease occurs most frequently in the male, usually in the same ratio as Dupuytren's contracture of the palm, although in the 16 cases reported by Pickren *et al.*, 6 were in males and 10 in females The age is usually lower than that of patients with Dupuytren's palmar contracture, most cases occurring under 30 years of age In a few instances the disease has been reported as a congenital anomaly It is frequently bilateral and not infrequently associated with other fibromatoses Pickren *et al* have reported 25 bilateral cases and 31 unilateral cases in the literature in which mention is made of this feature Fibromatosis of the palmar fascia has occurred in at least 65 of the reported cases of plantar fibromatosis Penile fibromatosis was associated with the plantar fibromatosis in only one of the reported cases. A familial relationship similar to that in palmar fibromatosis has also been noted to occur in fibromatosis of the plantar fascia Other factors which have been considered of etiologic significance are epilepsy (noted in 27 instances —by Lund and by Pickren *et al*), infection, hormonal disturbance, nerve injury, and coronary occlusion Most of these are unlikely causative factors, but some of the described associated disturbances may be manifestations of the desmoplastic diathesis

PATHOLOGY

The pathology is similar to that of the palmar fibromatosis, with the nodules extending plantarwise and rarely if ever involving the deeper structures In the early cases numerous young fibroblasts will be seen, and mitoses, sometimes rather numerous, will be noted in all phases of development. Rarely will an inflammatory cellular reaction be present With progression of the disease, the avascular, acellular fibrous-tissue component dominates the histologic topography

CLINICAL FEATURES

A characteristic symptom of a plantar fibromatosis is a subcutaneous nodular thickening, most frequently occurring in the middle portion of the medial half of the foot These nodules are singularly asymptomatic, but continuous standing such as endured by surgeons (see case report No. 6), will often produce tenderness As the fibrous proliferation invades the overlying skin, dermal invaginations occur Contractures of the toes may occur, producing a hammer-toe deformity, but this is extremely rare The explanation which has been advanced for the rarity of the toe contractures is the anatomic nature of the plantar fascia, which arises from the medial tubercle of the os calcis and extends between the plantar fat and the deeper muscles, tendons, and nerves to insert into the distal ends of the metatarsals associated with the aneural ligaments of the flexor tendons, with a superficial component inserting into the superficial transverse ligament Skoog has called attention to the fact that aponeurotic extensions to the toes are rudimentary and that the plantar aponeurosis is firmly fixed to the tarsal bones by means of fibers which descend at right angles from the main aponeurotic mass He stresses that this anchorage affects the static and functional activities of the foot Accordingly, contraction of the involved portion of the aponeurosis would be limited to that segment between skeletal anchorages and would

not be transmitted throughout the entire fascia with resultant phalangeal contractures as occurs in the hand.

DIFFERENTIAL DIAGNOSIS

The one condition which must be distinguished from a plantar fibromatosis is fibrosarcoma. The clinical appearance of the two conditions—a nonencapsulated, slowly growing, diffuse, somewhat asymptomatic, nodular enlargement—and the age groups are similar and could cause confusion in making the differential diagnosis The presence of mitoses in fibromatosis could frighten the pathologist into making a diagnosis of fibrosarcoma. There have been at least three amputations for plantar fibromatosis, two reported by Pickren *et al.* and one by Henry who amputated such a tumor because it adhered to the skin Pickren *et al.* state that in five of the nine slides referred to them, a diagnosis of sarcoma had been made or indicated They suggest that a case reported by Broders and called fibrogenic sarcoma, Grade I, with similar tumors involving the other foot and left arm may have been simply fibromatosis

A distinguishing factor which would permit a differential diagnosis is embraced by the fact that fibrosarcomas occur very rarely in this location Pickren *et al* have stated that only 2 verified sarcomas of this location have been recorded in the literature In our series of 39 fibrosarcomas, 2 occurred on the plantar surface of the foot. Recurrent nodules after local excisions should not cause concern as they merely reflect the incompleteness of the surgical excision. We have recently observed a sarcomatous degeneration of a plantar fibromatosis

Bizarre histologic changes may occur in a region of localized fibromatosis These consist of loss of polarity of the



Fig. 90. Low-power view of recurrent nodule with the surrounding fibrous tissue in a patient previously treated for plantar fibromatosis. The poorly defined borders of the lesion and it cellularity are evident indicating early fibrosarcoma (Case report No 6)

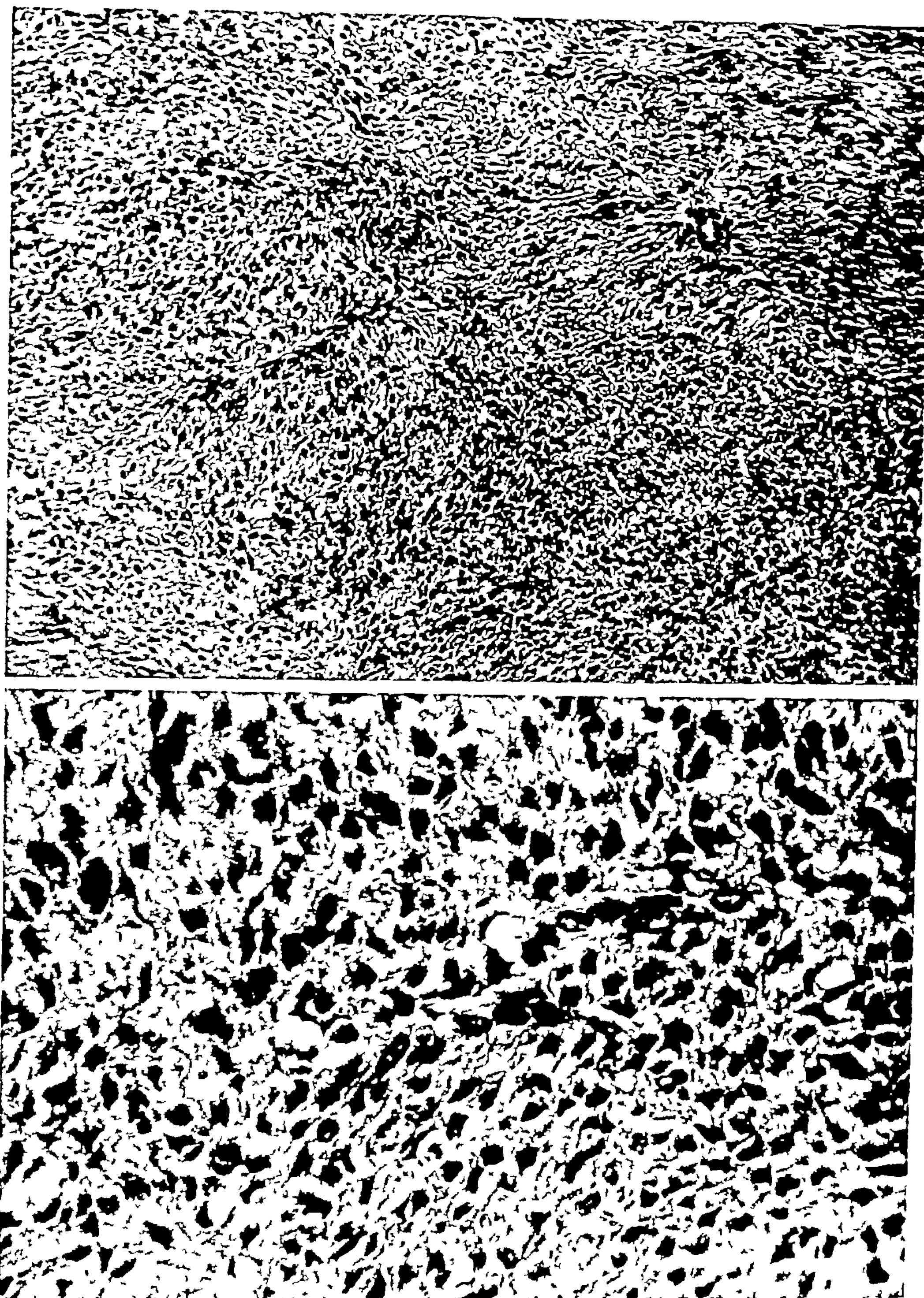


FIG 91 (*Upper*) Higher magnification of Fig 90 showing the irregularity in the shape and size of the fibroblastic type of cells There is no tendency for an orderly arrangement of the collagen fibers The arrangement of the chromatin granules within the nuclei is difficult to study in the sections obtained (*Lower*) High-power view shows the nuclei shrunken or pulled away from the surrounding protoplasm leaving white spaces They become triangular and polygonal in shape instead of fusiform All nuclear detail in the tumor cells is lost

cells, pyknosis of the nuclei, fibrillar degeneration, and at times atypical mitosis The following report of such an instance epitomizes the confusion attendant upon establishing an exact diagnosis when certain unorthodox histologic changes occur in plantar fibromatosis

CASE REPORT NO 6

V W, the patient, a 29-year-old physician, first noted a small nodule on the plantar aspect of the right foot two and one-half years before presenting himself to us for treatment Four months before we saw him a local excision of a small nodule was



FIG 92. Plantar fibromatosis treated by wide surgical excision.

performed under infiltration local anesthesia. A recurrence promptly occurred three and one-half months later and when the patient was first seen a 2 × 3 cm. subcutaneous nodule had developed in the sole of the right foot. It apparently originated in the plantar fascia it extended longitudinally and was adherent to the overlying skin in the region of a transverse scar from the previous local excision A wide local excision of the mass including a generous portion of the surrounding plantar fascia was effected. A second recurrence developed three years later it was also treated by a wide excision to include most of the plantar fascia. The histologic diagnosis of all specimens was fibroplasia developing to fibrosarcoma, Grade I The histologic features are presented in Figures 90 and 91

TREATMENT OF PLANTAR FIBROMATOSIS

The only satisfactory treatment of plantar fibromatosis is surgical excision Whether surgical excision is indicated for all patients suffering from such nodular overgrowths is questionable It is highly probable that many people with plantar nodules never seek therapy because most are asymptomatic. Toe contracture is seldom a complication. We have excised localized nodules with satisfactory results Recurrences should be more widely excised. For the more extensive overgrowths and for large ones which produce symptoms, excision of the entire plantar fascia is indicated An incision through the nonweight bearing portion of the foot will produce a minimal cicatrix. It is essential that the leg be immobilized and preferably elevated for from ten days to two weeks after operation. Weight bearing may induce bleeding or wound separation with a resultant painful scar Sufficient data are not available to adjudge critically the efficacy of x ray therapy tocopherol administration hormones (ACTH and cortisone) and other methods That these agents are not routinely indicated is represented by the good results following adequate surgical resection

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PEYRONIE'S DISEASE

Peyronie's disease represents a fibrositis involving the sheath of the corpora cavernosa of the penis, which may extend into Buck's fascia and the tunica albuginea. The corpus spongiosum is seldom involved The pathologic involvement may spread to the subcutaneous tissue and produce a brawny induration of the overlying skin. It presents as a discoid, brownish plaque involving usually the shaft of the penis The etiology is unknown, but it probably represents a localized manifestation of a fibroplastic diathesis Some of the etiologic factors advanced for this disorder include inflammation, compromise of the blood supply to the region, a replacement of elastic tissue with fibrous tissue, gout, and diabetes

When first described in detail by François de la Peyronie in 1743, he expressed a belief that trauma might be of etiologic significance (Although Peyronie is usually credited with having first described this entity, the belief has been expressed that the entity described by Ephémérides in 1687 is the same disease later discussed by Peyronie)

François de la Peyronie was so outstanding that he was nominated by King Louis XIV to be the perpetual president of the French Academy He did not accurately describe in his article "Some Obstacles Opposing the Natural Ejaculation of Semen" the condition commonly known by his name While Peyronie said that the disease of chronic fibrosing cavernitis occurred commonly in those "men who give themselves up to the vivacity of their temperament," Tuffier countered with "the age when the erection is only a vanity is very difficult to determine"

ETIOLOGY

That some form of acute or chronic irritation may be an etiologic factor is suggested by the fact that many patients suffering from this disorder give a history of having had such preceding lesions as acute gonorrhea or chancre, fracture of the penis during priapism or intercourse, stricture, or surgical trauma to the organ

The relationship of Peyronie's disease to other fibrositis is indicated by the fact that 3 of a series of 48 patients of Burford, Glenn, and Burford suffered an associated Dupuytren's contracture Polkey reported that of 549 patients, 22 had an associated Dupuytren's contracture In Scott and Scardino's series of 23 patients with Peyronie's disease, 6 suffered from Dupuytren's palmar fibromatosis

PATHOLOGY

The gross pathologic appearance is that of a glistening, pearly-grey to brownish nodular plaque measuring from 3 to 5 mm in thickness and from 3



Fig. 93. Peyronie's disease. Low-power photomicrograph demonstrating the markedly dense acellular hyalinization of the subcutaneous tissues of the penis.

to 5 cm. in diameter Its gross appearance is not unlike that of a keloid. Imbedded in the substance may be palpated small, stonelike foci which represent calcium deposition Foci of cartilage and bone have also been described

Microscopically the characteristic feature is the compact bundles of connective-tissue fibers A few fibroblasts may be noted scattered throughout and small thin walled blood vessels may on occasion be seen in infrequent numbers As a rule no inflammatory cellular infiltration occurs

CLINICAL FEATURES

Age

Peyronie's disease is essentially a disorder of middle aged males 88 per cent of the reported cases[1] were between 44 and 69 years of age The youngest patient of Burford's series was 22 and the oldest 84

Location

The fibrous plaque generally presents on the dorsum of the penis In a series of 85 reported cases 64 occurred on the dorsum, 9 on the lateral aspect, and 7 on the ventral aspect. In 5 patients multiple plaques were present.

Symptomatology

The symptoms in order of frequency complained of by the patients as reported by Burford *et al.* were as follows abnormal curvature of the penis, 80 patients (curvature upward 43 downward, 8 curvature to one or the other side, 21) lump on the penis 54 patients penile pain 40 patients no erection distal to the fibrous plaque 5 cases and inability to engage in intercourse 4 patients The attention directed to penile lesions is emphasized by the speed with which these patients sought medical care. Thus 60 (54 per cent) of 111 patients sought treatment within the first 6 months and 100 of these individuals sought treatment within a 12 month period

TREATMENT OF PEYRONIE'S DISEASE

The treatment has consisted essentially of surgical excision, various forms of irradiation, ranging from ultraviolet to gamma irradiation and more recently the use of tocopherols Surgical excision alone is apparently the most unsatisfac-

tory as recurrence is the rule. Burford and his colleagues prefer the use of a radium plaque and have observed good results to occur following its use, with dosages which have ranged from 50 to 325 mgh (the latter for multiple lesions) The average dose which they have advocated is 120 mgh These authors are now combining the use of a tocopherol (Tocopherex) with the radium plaque and believe that this combined therapy enhances the incidence of beneficial responses They claim that of 124 patients treated by them, about 90 per cent have enjoyed an excellent response Only 3 patients suffered postoperative complications—a chronic weeping, indolent ulcer which was satisfactorily excised in 2 cases

Scott and Scardino have reported good results with the use of vitamin E in the treatment of Peyronie's disease. Attention was first directed to the use of this agent in 1941 by Steinberg, who noticed excellent improvement following the use of tocopherols in a patient with muscular dystrophy He noted a similarity in the pathology of nutritional muscular dystrophy and primary fibrositis In both conditions he also noticed a decrease in the excretion of creatine After the use of mixed tocopherol, clinical improvement and an increased creatine excretion were noted following the treatment of both conditions

Since 1947 Scott and Scardino have treated 23 patients with Peyronie's disease by administering tocopherols Their dosage consisted of a total daily dose of 300 mg mixed tocopherols or 200 mg of synthetic alphatocopherol They report the following results In patients with curvature of the penis, complete disappearance of the curvature was noted in 4, marked subsidence in 4, moderate subsidence in 4, no change in 2, and 2 patients were lost to follow-up All patients stated that any pain which they had had disappeared following therapy Of the 13 patients with intercourse interference, 10 were able satisfactorily to resume the act, and 3 could not Fibrous plaques became soft and diminished in size markedly in 6 patients, moderately in 15, and no change occurred in 2 An interesting feature was the authors' remarks concerning the effects upon an associated Dupuytren's contracture in patients with Peyronie's disease. Of 6 such patients, 1 enjoyed marked improvement, there was moderate improvement in 3, and in 2 no change was observed in the Dupuytren's contracture

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CONGENITAL STERNOCLEIDOMASTOID TUMOR (CONGENITAL MUSCULAR TORTICOLLIS)

Congenital muscular torticollis is a fibrous replacement of the muscle fibers of the sternomastoid muscle It is not a true neoplasm as such but is a localized swelling of muscle The involvement may be either diffuse and involve the entire sternomastoid muscle, or it may be localized, producing a rounded, diffuse, semifirm mass which gives the clinical impression of a neoplasm The mass usually presents itself within one to two weeks after birth, gradually increases in size, and reaches its maximum growth at the first month after birth. It may then either remain stationary or it may remain quiescent temporarily then gradually regress If regression does occur it is usually completed within the



FIG. 94. A. Tumor of left sternocleidomastoid muscle at 5 weeks of age. B C Low and high-power photomicrographs of excised tumor (Courtesy Dr F A. Chandler and Bull. Hosp. Joint Dis 14 158, 1953.)

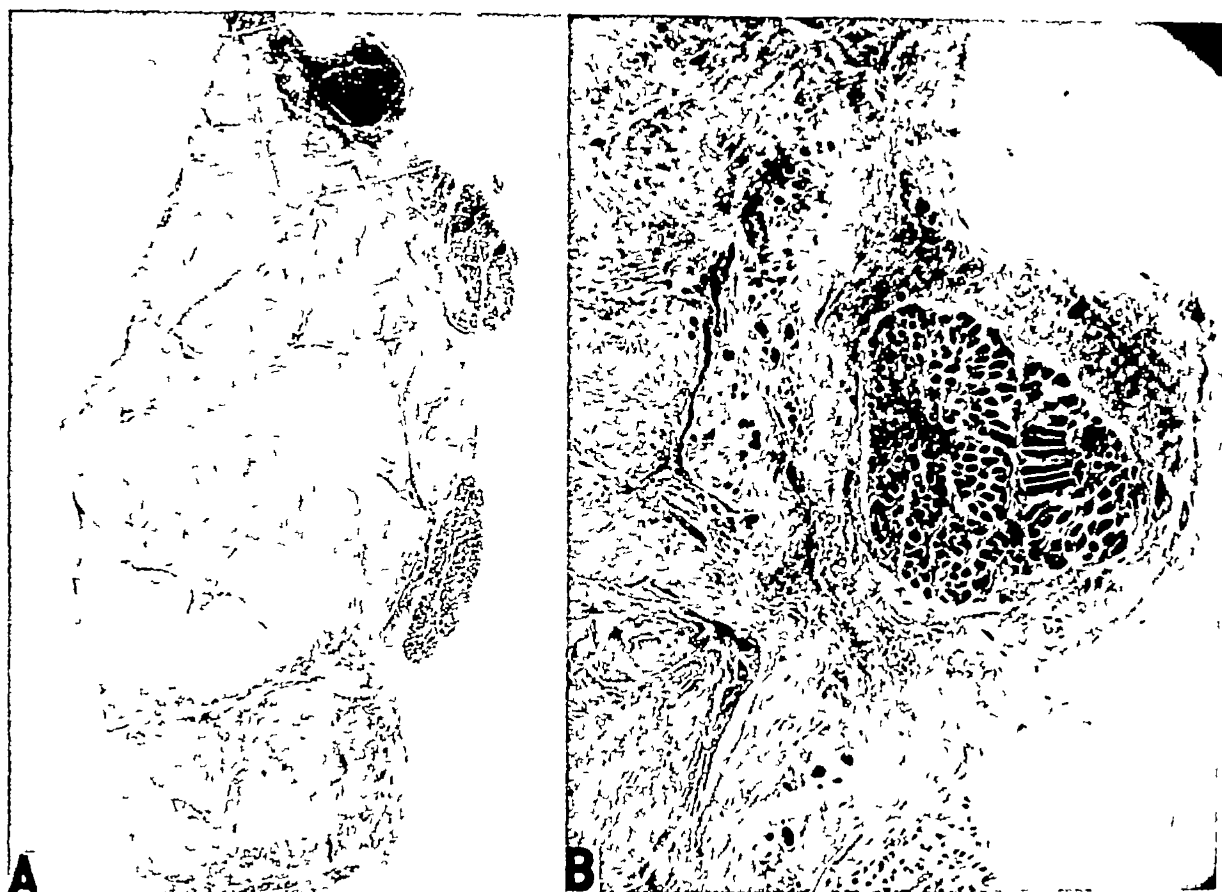


FIG 95 *A* Microscopic section of excised tumor showing muscle fibers at periphery and scattered throughout *B* High-power view of boxed area Illustrating a localized section, apparently normal muscle persists This is rather characteristic of congenital muscular torticollis (*Courtesy,* Dr F A Chandler and Bull Hosp Joint Dis *14* 158, 1953)

first six months When one portion of the muscle is involved, there may be no torticollis present or it may be minimal However, if the entire sternomastoid muscle is involved, the torticollis may be marked, this becomes further aggravated as growth progresses The head is directed toward the affected side with the face drawn to the opposite side The associated changes consist of an alteration in the level of the eyes, the clavicle and shoulder become elevated, and the skull usually becomes diminished in its frontal-occipital diameter with increased prominence of the mastoid process As the condition persists, irreversible changes occur

Congenital muscular torticollis is rare It has been estimated to occur about once in 150,000 births It occurs with the same frequency in both sexes and in all races As far as can be determined, there is no predilection for one or the other side of the neck Rarely, it is bilateral, and occasionally other associated congenital deformities such as clubfoot, maldevelopment of the ear, etc, may be present

Bick has presented an interesting historical account of this abnormality He described an apparatus for correcting wryneck developed by d'Aquapendente (1537–1619)

In 1670 Van Roonhuysen theorized that abnormal pressure on the head *in utero* produced the deformity and showed that torticollis existed *in utero* Chandler records four experiences of roentgenographic evidence of intrauterine torticollis

In 1685 Isacius Minnius performed a tenotomy for torticollis In 1875 Taylor described an "induration of the sternomastoid muscle or sternomastoid 'tumor'" He vividly described the infiltration of fibrous tissue between the muscle bundles with gradual degeneration of the muscle

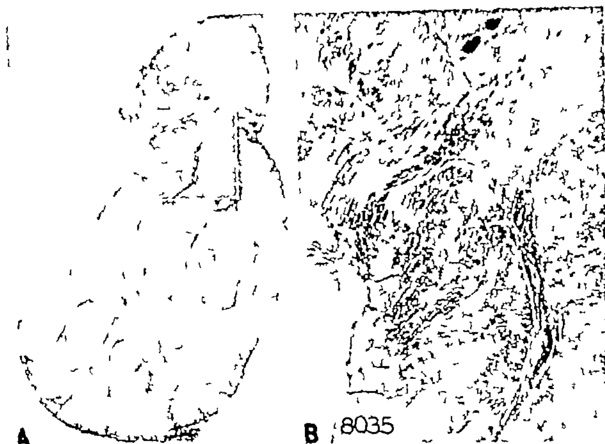


FIG 98. Microscopic section of tumor low and high power illustrating the partial and at times complete degeneration of muscular fibers and replacement by fibrous tissue (*Courtesy* Dr F A Chandler and Bull. Hosp Joint Dis. 14 158 1953)

ETIOLOGY

The etiology is unknown. Neurogenic disturbances have been listed as causative factors The association of this disorder with breech presentation and difficult and prolonged labor suggests a traumatic relationship to this entity

Heredity is important, but because of the rarity of this disorder it is hard to analyze the specific geneologic relationship The occurrence of muscular torticollis in identical twins (Stevens) serves to support the hereditary relationship In a review of 101 cases by Chandler and Altenberg two of the infants mothers also had muscular torticollis, and a brother of one had a fibrous cord replacing the sternocleidomastoid muscle Von Lakum reported three children of four siblings to have congenital muscular torticollis

From the evidence at hand, it must be assumed that this congenital deformity represents a localized manifestation of a fibroblastic diathesis with trauma of some nature possibly superimposed

PATHOLOGY

The tumefaction consists of a diffuse swelling of a portion of the muscle or at times of the entire muscle On occasion separate tumors may be encountered The swelling presents a smooth, firm, freely movable mass unattached to the overlying skin, completely discrete from all surrounding tissues, with no alterations of any nature in the contiguous tissues On gross examination the diseased portion of the muscle appears as a dense firm, ropy surface which varies from soft musclelike texture to hard woody consistence. The characteristic microscopic appearance is the degeneration of the muscular fibers with alterations varying from partial degeneration to complete destruction of the muscle fibers Scattered throughout are small

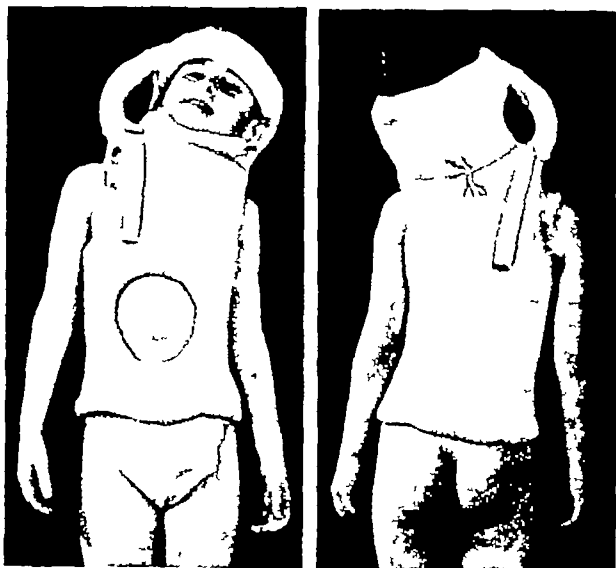


FIG 97 Cast and shoulder strap employed for maximum correction in older children (*Courtesy*, Dr F A Chandler and Bull Hosp Joint Dis *14* 158, 1953)

localized sections in which apparently normal muscle persists These are usually found at the periphery Replacing the muscular element of the sternocleidomastoid muscle are various forms of fibroplastic infiltration which vary from numerous proliferating fibroblasts, arranged in orderly fashion, to other sites where dense cartilaginous fibers dominate the histologic topography This represents essentially fibroblastic replacement of the sternocleidomastoid muscle There is no evidence of any malignant neoplastic alteration

TREATMENT

The treatment of congenital torticollis varies with the severity of the deformity In infants with a minimal change and no torticollis, no therapy is indicated If there is a tilt of the head which appears to increase with growth, resection of the entire sternocleidomastoid muscle is the procedure of choice The exact time when operation should be performed has not been definitely determined Some advocate resection of the muscle within the third week of life Although these children tolerate the operative procedure well, it is wiser to delay operation, observe the natural history of the swelling, and to determine whether or not it regresses Others advocate delaying until the pathologic change has run its course, with excision of the muscle at a later date, usually at the age of 5 to 7 years. After operation, immobilization with a small plaster splint may be indicated In the majority of instances the removal of the muscle will result in a normal anatomic and functional change. Careful postoperative care is essential Once irreversible changes have occurred and the patient has become accustomed to the altered position of the head and neck, removal of the muscle is seldom accompanied by improved position of the skull These changes usually become irreversible at about puberty.

Hulbert has reported 100 cases of congenital torticollis and 117 with sternomastoid tumor From these he separates congenital postural torticollis, which is present at birth and not associated with tumor He considers it transient and requiring no treatment Four-fifths of the sternomastoid tumors resolve spontaneously and leave no deformity, hence, in his opinion, excision is not justified in infancy

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was immobilized in a rigidly flexed position with the head twisted toward the right because of involvement of the sternomastoid muscle

Similar cases have been reported by Price in a 3½-year-old girl, by Schwab *et al* in a 14-year-old Negro boy who died 15 months after onset, and by Blau in a 15-year-old girl who lived for more than 20 years with her affliction

Burton, Cowan, and Miller have reported that three cases are listed in the literature in which the disease had its onset in adult life Schwab *et al* question whether these are true cases of progressive myositis fibrosa

ETIOLOGY

The etiology is unknown Various theories have been advocated which vary from trauma during birth with hemorrhage into the muscles to congenital abnormalities. The rarity of this condition precludes any means of establishing an inherited susceptibility The frequent occurrence of this disorder early in life would serve to identify progressive myositis fibrosa as an inborn error of the metabolism of connective tissue

PATHOLOGY

Progressive myositis fibrosa is essentially a primary disease of the fibrous tissue rather than an abnormality of the muscles The histologic feature is marked fibrous-tissue hyperplasia Increase in the fibrous-tissue elements are usually first noticed about blood vessels Subsequently all the fibrous-tissue components of muscle proliferate with fibroplastic invasion into the muscular elements The muscle fibrils undergo hyaline and granular degeneration and are gradually replaced by connective-tissue fibers.

Some investigators believe that progressive myositis fibrosa is a preosseous stage of generalized myositis ossificans, because in the latter affliction the replacement of the diseased muscles by fibrous-tissue elements usually precedes the stage of ossification The observation that ossification does not occur in certain patients afflicted with progressive myositis fibrosa would serve to separate these two conditions as distinct entities

As a rule there is no inflammatory reaction associated with progressive fibrositis Some have described a round-cell infiltration, but this feature is not characteristic

Chemical examination of the muscles has revealed nothing characteristic except some decrease in the creatine content

CLINICAL COURSE

The patient usually shows progressive and rapid involvement of numerous muscle groups, generally within the first five years of life. Despite the rapidity of the muscular involvement, the patient usually suffers little interference with his normal health There is complete absence of pain or tenderness Fever is not present In some instances the disease may progress rapidly, but the characteristic course is one of exacerbations and remissions During the period of remission, there may be some return of function The involved muscle will react to faradic current but in an abnormally defective manner Under anesthesia there is no relaxation of the afflicted muscle, and no increased range of motion can be obtained even with the use of muscle relaxants This is understandable since the muscle is replaced by fibrous tissue

METABOLIC DYSFUNCTION ASSOCIATED WITH PROGRESSIVE MYOSITIS FIBROSA

Creatinuria is usually a characteristic finding in patients with myositis fibrosa Normally children excrete creatine in the

urine until the age of puberty after which only negligible quantities are found in the urine. Creatinine urinary content increases with increased age in the developing child and young adult In patients with myositis fibrosa, the quantity of creatine in the urine remains high while the creatinine content is proportionately diminished. These biochemical alterations are interpreted to represent evidence of muscle degeneration

DIAGNOSIS

Progressive myositis fibrosa is to be distinguished from progressive muscular dystrophy Although the end stages of both of these diseases reveal marked degenerative changes in the muscle with replacement by fibrous-tissue elements, it would appear that in progressive myositis fibrosa the dominant pathologic change is in the fibrous tissue element whose marked hyperplasia infiltrates the muscle bundles with secondary degeneration of these bundles In muscular dystrophy the degeneration of these muscles is primary with secondary replacement of both fat and fibrous-tissue elements Increased numbers of the nuclei of the sarcolemma occur in muscular dystrophy Certain radiologic changes in long bones have been described by Epstein and Abramson in muscular dystrophy The fact that similar changes occurred in an 11 year-old boy with progressive myositis fibrosa described by Stewart and Macgregor led these authors to believe that progressive myositis fibrosa is one form of progressive muscular dystrophy

TREATMENT

There is no known treatment for this affliction Vitamin E and tocopherols have been advocated but satisfactory results have not been obtained Blau reported symptomatic improvement and restraint in the progression of the disease with the use of glycocoll but the benefits were transient and limited. Physiotherapy is about all that one can offer

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MYOSITIS OSSIFICANS PROGRESSIVA*

Myositis ossificans progressiva is a disease characterized by a deposition of bone in muscles or about their insertions The lesion involves primarily the aponeurosis and fascial connective tissue, any muscular changes being secondary and degenerative Aberrant osteogenesis, however, is not limited to the skeletal system and voluntary muscles True bone formation has been reported as occurring in the meninges, brain, arteries, lungs, lymph nodes, stomach, kidneys, ureter, bladder, and skin, as well as in benign and malignant tumors.

Although Guy Patin, in describing the woman who turned to wood, reported the first case of myositis ossificans in 1692, it was not until the advent of the roentgen ray as a diagnostic aid that the disease really became an important clinical entity and medicolegal question Freke in 1740 and Copping in 1741 reported cases similar to that of Patin In 1860 Bulhak described two types of the disease, a progressive type and an isolated or circumscribed type Von Dusch in 1868 gave the disease its name, and the following year Munchmeyer collected 12 cases from the literature and gave an exact description of the disease During the last four decades the literature has abounded in case reports and papers on the subject Yet the incidence is undoubtedly higher than has been reported, since frequently the condition is discovered incidentally after having been present for many years About 160 cases of myositis ossificans progressiva have been recorded in the literature

The two types of the disease described by Bulhak have been subdivided by later writers Shipley, Gruca, and others have given excellent discussions of this classification It will suffice for the purpose of this exposition merely to tabulate them.

1 Myositis ossificans conscripta, generally known as the muscle osteoma, appears in sites of repeated slight injuries or irritation

2 Myositis ossificans, also localized to one site of the body, develops as the result of a variety of causative factors, the most common of which is a single, severe, closed trauma

3 Myositis ossificans localized in a single muscle without any history of trauma or other known causative factor is usually discovered accidentally

4 Myositis ossificans progressiva usually begins in the muscles along the spine and gradually spreads until it involves all the muscles of the body, possibly with death resulting because of its interference with respiration It is usually associated with defective anatomic and physiologic formations, mostly of fingers and toes This discussion will primarily deal with this progressive type since it represents a generalized disruption of the connective-tissue system

ETIOLOGY

Numerous theories have been advanced to explain the development of these localized bony growths Whether it is due to an implantation of periosteum in muscle, an escape of osteogenic cells from the periosteum, an ossifying hematoma, or just a metaplasia of connective-tissue cells, it must depend on some additional growth-regulating factor and/or peculiar local reaction of the tissue involved Were this not true, myositis ossificans would be a common sequence to fracture Shipley points out that the systemic condition of the patient does not appear to be significant Normal values for blood calcium, phosphorus, and phosphatase have been reported There has been no evidence of parathyroid or of

* In collaboration with Ralph R Braund



FIG. 98. Congenital myositis ossificans progressiva. (*Upper*) In this view of the lumbar muscles, note the large plates of ossified tissue to the left of the midline and extending from the eleventh dorsal to the fifth lumbar vertebra. (*Lower*) Calcified plaques found in the posterior cervical muscles. (Pack and Braund, J.A.M.A. *119* 776 1942.)

other hormonal imbalance A shift of alkalinity of the tissue fluids, the growth of connective tissue cells, and the activity of an enzyme that splits phosphoric acid from organic compounds have been cited by Wagner as possible factors influencing the development of these bone tissues. Hirsch and Morgan suggest the possibility of an individual diathesis or dyscrasia. Gruca demonstrated fibrocartilage to be a normal constituent in

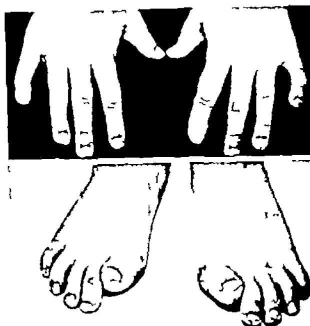


FIG. 99 The same patient as in Fig. 98, showing other congenital deformities. (*Upper*) Appearance of the hands, showing microdactylia in thumbs and fifth fingers. Roentgenograms demonstrated anomalous epiphyseal development in both hands. (*Lower*) Appearance of the feet, showing deformity similar to hands. Roentgenograms revealed the most noticeable deformity in the first metatarsals. These deformities are considered pathognomonic for Meyenburg's disease. (Pack and Braund, J.A.M.A. *119* 776 1942.)

cases in which traumatic ossification occurs Whatever the factors may be, it is generally agreed that the plates of bone arise from the connective tissue or indirectly from the connective tissue through an intermediary cartilaginous stage No group of skeletal muscles is exempt. In myositis ossificans progressiva, there is associated developmental defects (as hallux valgus or microdactylia) in 75 per cent of the patients This suggests a prenatal and possibly inherited derangement of mesenchyme.

CLINICAL FEATURES

Myositis ossificans progressiva, although a similar pathologic process to the localized forms is distinctly and etiologically separate from the other types Rosenstirn noted a group of characteristic symptoms which sharply differentiated this condition as a clinical en-

tity These characteristic features are (1) the ossification of muscles without any apparent cause, traumatic or otherwise, (2) the manifestation of the disease as a congenital one or one appearing early in life, (3) the progressive course of the malady, unaffected by therapeutic efforts, embracing in some of the most advanced cases nearly the entire voluntary muscular system, and (4) its association with symptoms of defective anatomic and physiologic formation, mostly of fingers and toes Barr believes that this disease results from a true metaplasia of connective tissue to bone Rosenstirn collected 119 cases of myositis ossificans progressiva from the literature and added one of his own.

Occasionally myositis ossificans may behave like normal bone in being subject to attack by further pathogenic processes Cone described a case resembling osteitis fibrosa cystica A suppurative process analogous to acute hematogenous osteomyelitis has been reported as developing in myositis ossificans Shipley found four cases recorded in the literature of the development of osteogenic sarcoma in preexisting myositis ossificans traumatica Pack and Braund have reported two cases in which osteogenic sarcoma developed in preexisting myositis ossificans circumscripta and a third case in which myositis ossificans progressiva was associated with a sarcoma developing in the muscles of the back (See pp. 337–341)

Progressive growth with associated ossification of muscles continues, until most of the muscles from the skull to the feet may be involved It occurs most frequently in boys but the disease is so rare that it is impossible to establish any sexual ratio It is said to occur mainly in Anglo-Saxons

DIFFERENTIAL DIAGNOSIS

Some believe that *myositis fibrosa* is not a separate entity but a preosseous stage of myositis ossificans progressiva, since ossification of the muscles is preceded by a fibrositis stage The bulk of evidence suggests that these represent separate entities although an abnormality of mesenchyme is a common denominator of both diseases

Dermatomyositis affects the extremities and later the trunk Fever, sweating, and splenomegaly occur Some believe there is a relation between dermatomyositis and myositis ossificans

TREATMENT

No satisfactory treatment for this disturbance exists Numerous therapeutic agents have been utilized, these include ketogenic and low-calcium diets, x-ray therapy, parathyroid injections, vitamins, surgery, etc Beryllium carbonate has been given in an effort to lower the phosphorus level of the blood and to prevent calcification It has not been very successful Maudsley removed a segment of bone and followed this with deep x-ray therapy No recurrence developed, which encouraged him regarding this form of treatment (See Figs. 164–172 for illustrations of myositis ossificans progressiva and tumors arising within ectopic bone)

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RADIATION FIBROMATOSIS

The usual reaction to radiation in moderate dosages consists of an increased vascularity of the irradiated region followed by an increased fibroblastic activity with resultant fibrosis of the region Irradiation produces tissue inflammation followed by a fibrotic reaction Collagen the most sensitive of the connective-tissue elements, becomes thickened and pale, and with larger doses loss of fibrillation or actual necrosis may ensue The mature fibrocytes succumb and resident fibroblasts assume bizarre shapes (Fig 100) There then occurs in the region evidence of fibroblastic invasion which actively deposits



Fig 100 Radiation fibroblast (*Courtesy Dr George K Higgins*)

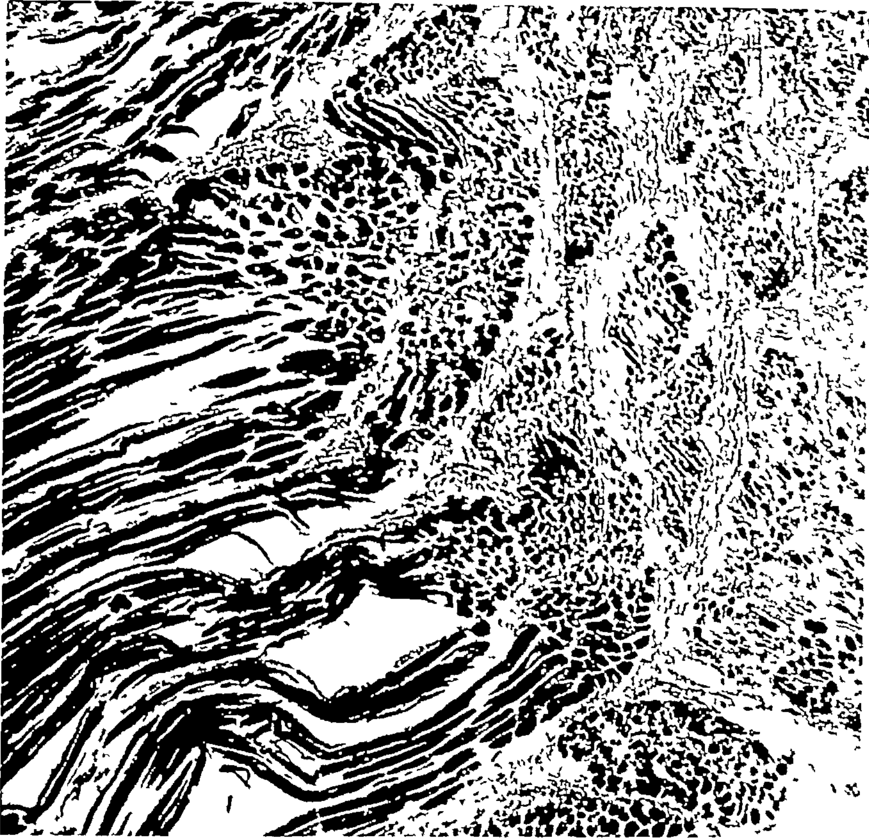


FIG. 101 Atrophy and fibrosis of striated muscle from radon implantation 5 years previously (*Courtesy,* Dr George K Higgins)

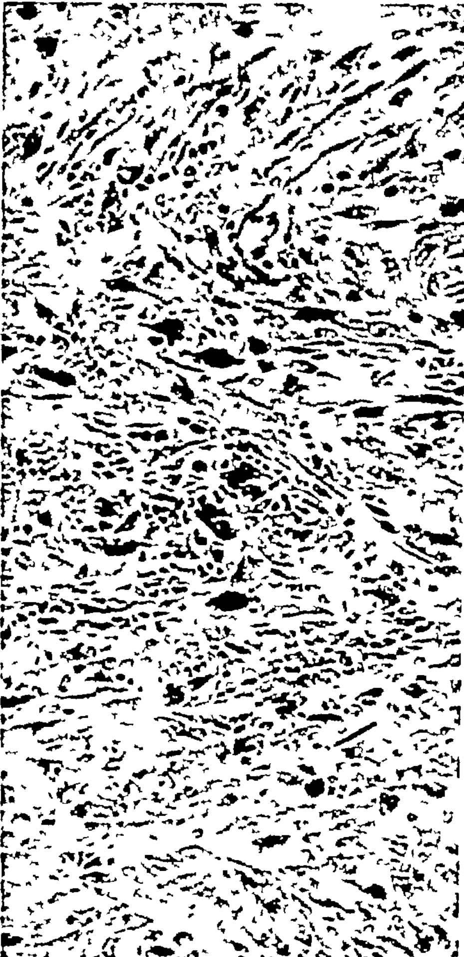


FIG 102 Marked fibrosis in a melanoma removed 3 months after intensive irradiation (Courtesy, Dr George K Higgins)

an abundance of flat collagenous strands that then undergo contracture. The combination of vascular damage with marked fibrosis results in a late effect of irradiation of an acellular avascular

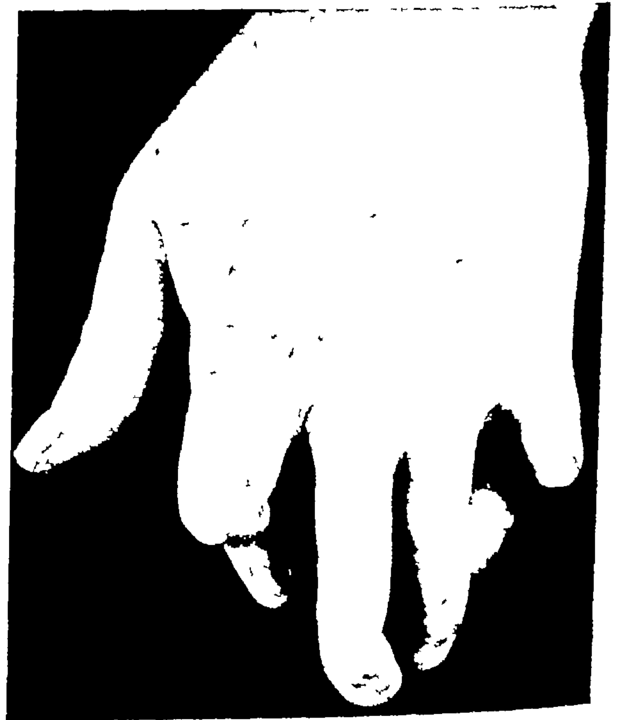


FIG 103 Advanced stage of radiation fibrosis producing severe contracture in a roentgenologist who was constantly exposed to roentgen rays

fibrotic tissue with thin overlying epidermis In certain instances especially after large doses of irradiation this fibrous reaction may be so marked as to dominate the regional anatomy It is not rare for the fibrous tissues to break down and become secondarily infected This irradiation fibrosis will persist permanently Pettit *et al* have presented four patients who received prolonged irradiation many years before the development of fibrosarcomas in these regions, and they have interpreted the development of the fibrosarcoma to be due to fibrosis as the result of irradiation Other examples of fibrosarcoma developing in irradiated regions have been recorded in the literature

Sarcomas have been produced experimentally by Lacassagne and Vinzent after inflaming the legs of animals by injecting the streptobacillus caviae and at a later date by irradiating these animals Each of the rabbits so treated developed various forms of sarcoma including fibrosarcoma rhabdomyosarcoma, and osteogenic sarcoma Simple irradiation to the legs of animals did not produce sarcomas From these animal experiments it would seem that irradiated tissue which had undergone fibromatous changes with superimposed chronic inflammatory change (the result of increased susceptibility to infection in these damaged tissues) would be a causative factor in the production of a malignant tumor

These observations focus upon the danger of radiation fibrosis and emphasize the importance of prophylaxis by the judicious administration of irradiation, adhering strictly to suitable dosage time factors

TREATMENT OF RADIATION FIBROSIS

Advanced radiation fibrosis, especially if it is in the region of most constant irritation, the hand, or if it becomes secondarily infected, should be surgically excised, and suitable reconstructive surgical procedures should be instituted

Fibrosarcomas arising in tissue previously irradiated are treated as any fibrosarcoma but it is considered advisable to resect a large margin of the non sarcomatous irradiated tissue

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BENIGN TUMORS

FIBROMA

The simple term *fibroma* describes an entity which is a maze of uncertainty inasmuch as the exact histologic classification, and consequently the nosologic position of fibromas, awaits elucidation In fact, it has not been definitely determined whether benign neoplastic proliferation of fibroblasts occurs Fibroblastic proliferation is observed, the result of a wide variety of stimuli which vary from minimal physical or chemical irritation to the widespread replacement of a major portion of the body musculature by fibrous-tissue invasion as occurs in progressive myositis fibrosa The problem of defining a pure, self-limiting, nonmetastasizing, neoplastic proliferation of fibroblasts (the fibroma) is rendered difficult, especially in the presence of the nonneoplastic, nodular proliferation noted in certain of the fibromatoses (palmar or plantar fibromatosis) The situation is further compounded by neoplastic changes occurring within certain of the fibromatoses

A most interesting feature of the fibroma is the observation that it occurs with extreme rarity in the soft somatic tissues, where fibrous tissue is most abundant Its occurrence is most frequently noted within parenchymatous tissue

It may occur in the pure form, *i e*, containing exclusively fibrous-tissue constituents, as noted in the kidney When it develops in the ovary, it produces the bizarre clinical syndrome of hydrothorax (Meigs's syndrome) More frequently fibromas exist as mixed tumors, such as fibroadenoma of the breast In such situations it is difficult to discern whether the fibrous-tissue overgrowth is a nonneoplastic stromal accompaniment to an adenomatous neoplasm such as occurs in malignant counterparts, the scirrhous carcinoma, or whether the fibroadenoma is a truly mixed neoplasm consisting of both ectodermal and mesodermal components The frequently occurring fibromyoma of the uterus represents an example of a benign neoplastic overgrowth of two mesodermal derivatives, muscle and fibrous tissue Certain fibroblastic tumors of the soft somatic tissues, which are grossly invasive but occur in sites other than the abdominal wall and tend to be benign on histologic criteria, have been termed *desmomas*

Fibromas occur in all species of animals and even have a propensity to form within different breeds within a specie The Boston terrior has a high incidence of fibroblastic tumors, and the fox terrier also shows a definite tendency to be afflicted with fibroma and fibrosarcoma, which are commonly located on the extremities, such as the elbow and thigh, and at the gingival margins, in the thorax, abdomen, and the vagina Occasional sites are the orbit, eyelid, etc.

Inasmuch as fibromas rarely occur within the soft somatic tissues of the human, this chapter will be limited to a brief presentation of certain features of fibromas which occur *in relation* to the soft somatic tissues

Skin and Subcutaneous Tissues

There are several tumefactions of the skin or subcutaneous tissues of fibro-

blastic origin The *fibroma durum* represents small, firm overgrowths of fibrous tissue within the skin itself. Pedunculated fibromas occur within the skin, the so-called *fibroma molle* which are believed by Stout to be congenital malformations. These are essentially an overgrowth of epidermal structures containing a fibrous-tissue core.

The cutaneous and subcutaneous fibromas enjoy a large and diversified nomenclature because of the various theories regarding their pathogenesis Some of the terms used to designate these tumors are *fibroma simplex, nodules cutaneous fibrome en pastille dermatofibroma lenticulare histiocytoma cutis* and *nodular subepidermal fibrosis* The three theories cited by Gentele regarding their origin are (1) they are true fibromas (2) they represent postinflammatory fibromatous reaction, and (3) they are forms of histiocytomas. It is probable that additional study will serve to differentiate the three different forms

Small, locally infiltrating fibromas also occur within the skin Stout labels these tumors fibromas if their size is limited to a diameter of from 2 to 3 cm If a larger size is attained, he believes they should be called dermatofibrosarcoma protuberans (see p 238) and if they are multinodular they should be classified as fibrosarcomas The well known neurofibromatosis of von Recklinghausen s disease is another neoplastic entity which involves the skin and subcutaneous tissues and in which fibrous tissue is admixed with neurilemmoma and nerve tissues

Keasbey has recently described a fibroblastic entity which she terms *juvenile aponeurotic fibroma* (*calcifying fibroma*) These are present in the palms of children as painless fixed masses which are not sharply delineated and not attached to the overlying skin Contractures are not present. Roentgenograms reveal a radiopaque mass with no osseous deformity Fine stippling of focal calcification may occur She describes the pathology as follows

> The hallmark of the juvenile aponeurotic fibroma is the peculiar cell type of which the tumor is composed Unlike the usual fibroma, in which one sees inconspicuous greatly elongated, fusiform nuclei enclosed in long, slender fibrillar cell bodies the picture in the aponeurotic fibroma is dominated by numerous large, darkly staining plump oval nuclei. These nuclei appear somewhat vesicular in that a narrow margin of chromatin is always found beneath the nuclear membrane. This however is somewhat obscured because the entire nucleus is chromatic owing to a rather characteristic reticulation of the chromatin which often takes on a vague stepladder distribution or a mulberry vesiculation. One to three very small blue-staining nucleoli may be present but because of their small size, they are inconspicuous The nuclei are strikingly similar one to another Rarely a giant nucleus is seen Sometimes certain nuclei appear to be round rather than oval. In areas of compression the nuclei may be somewhat elongated and irregular in contour Mitoses are not obvious
>
> In ordinary sections stained with hematoxylin and eosin no cell bodies are discernible enclosing these nuclei. They appear to lie on a sheet of faintly fibrillar pink staining matrix resembling collagen With special stains, one is surprised to see that the nuclei are surrounded by fairly abundant halo-like, rounded-oval cell bodies. The cytoplasm appears clear homogeneous, and almost entirely chromophobic with even the cell membrane failing to show any distinct affinity The stroma is seen to consist of sheets of closely packed, wavy collagen fibers Reticulin is scanty except in the characteristic areas of calcification later to be described. Here a heavy production of reticulin is seen, and in these areas copious exudation of mucopolysaccharides can be demonstrated by metachromatic and colloidal-iron staining methods.
>
> The second distinctive feature of the calcifying juvenile aponeurotic fibroma lies in the fact that all the cells appear to be



FIG 104 Delamater's case of retroperitoneal lipoma This case has also been described as a retroperitoneal fibroma (*Courtesy, Cleveland Medical Gazette*)

oriented in one direction They appear to be a sheet of cells all pouring forth in one plane This is in sharp contrast to most fibromas In the common cutaneous fibroma, for example, the cells are characteristically haphazard in arrangement These have been described as "curly" fibromas The arrangement of the cells has been likened to a pile of spilled matches or jackstraws that head in every conceivable direction Again, in the larger, more deeply situated fibromas, a prominent pattern of intersecting and intertwining fasciculi is the rule, often producing a more-or-less pronounced "herringbone" effect In sharp contrast to other fibromas, the prominent nuclei of the aponeurotic fibroma all tend to be parallel to one another, some further ahead, some behind, none crowding, but all appearing to grow in one sheetlike plane It is the prominence of these characteristic nuclei and their striking parallel orientation that are the distinguishing microscopic features of this tumor [*]

Whether these nodules are truly neoplastic or represent an expression of fibromatosis, subdivided as juvenile fibromatoses by Stout, awaits elucidation

[*] L E Keasbey Juvenile Aponeurotic Fibroma (Calcifying Fibroma), Cancer, vol 6, p 338, 1953

FIBROMAS OF THE UPPER RESPIRATORY SYSTEM

Juvenile nasopharyngeal angiofibroma (see p 212) represents a composite fibromatous and angiomatous overgrowth Certain *nasal polyps* probably represent benign fibromas of this region, although most of them are overgrowths resulting from an inflammatory reaction Ewing describes the *choanal polyp* which arises from the posterior nasal orifice, usually from the mucosa of an accessory sinus It has a long fibrous pedicle and can attain large size These polyps are more cellular and more prone to recurrence than the usual nasal polyps *Polyps of the vocal cord* represent a situation similar to the nasal polyps, most of them representing an inflammatory overgrowth. In other instances a true fibroma of this organ occurs.

OSSEOUS SYSTEM

Fibromas of the bone and periosteum occur An example of this is the non-ossifying fibroma of bone.

FEMALE GENITAL TRACT

The fibroma of the ovary mentioned previously is usually very cellular and may reach a huge size Strangulation by torsion may occur

Vulvar fibromas are said to be quite common, which is surprising because the labia majora are composed mainly of fat It is believed that most of the vulvar fibromas arise from fibrous tissue within the pelvis or along the course of the round ligament Buckner in 1851 described a vulvar fibroma which is reputed to have weighed 268 lbs. It is stated that when this woman died, she could not be placed in the coffin, and Buckner was called in to resect the tumor so that the body would fit into the casket (*Novak*)

Fibroma of Tendon Sheath

This entity has been described rather infrequently Geschickter and Copeland recorded 30 cases Whether these tumors represent true fibromas or whether they are a fibrous metaplasia of the synovial cells and thus are a fibroblastic counterpart of the giant-cell tumors of tendon sheath is difficult to determine. The constant association of connective tissue with synovial cells in synovial sarcomas would suggest that the fibromas of tendon sheaths represent a fibrous metaplasia

Other Fibromas

Any combination of fibrous tissue with any of the other mesenchymal derivatives can occur with the production of such tumor entities as fibrolipomas angiofibromas, myxofibromas etc.

TREATMENT OF FIBROMAS

Treatment is exclusively surgical extirpation, and the results are uniformly excellent There would seem to be frequent recurrences, however because of the difficulty in distinguishing fibromas on the one hand from fibromatosis wherein there is renewal of fibrous proliferation in the region of excision and on the other from fibrosarcoma with its tendency to recur locally

Several instances of fibromas undergoing malignant transformation have been recorded (Wilson) These observations emphasize that fibromas cannot be considered innocuous lesions which may remain untreated.

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JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

The juvenile nasopharyngeal angiofibroma is a benign tumor entity, unencapsulated, usually noninfiltrating, originating in the posterior nares or nasopharynx, and composed of mixed angiomatous and fibrous tissues It occurs almost exclusively in adolescent boys and may involute spontaneously with full sexual maturity Martin, Ehrlich, and Abels call attention to certain sex-endocrine factors which they consider of etiologic significance The effects of the alteration of endocrine balance upon the vascular components of certain tissues, particularly sex-linked tissues, have been demonstrated

This tumor is similar to hypertrophic hemangiomas of infants and children, angiomatous fibrous tumors which may occasionally involute with the development of the child. Nasopharyngeal angiofibromas rarely occur after puberty, and one case reported by Finerman in a female was not accepted by Sternberg

The name *juvenile nasopharyngeal fibroma* was coined by Chaveau in 1906 Martin, Ehrlich, and Abels in a report of 29 cases from the Memorial Hospital have clarified the clinicopathologic features of this tumor Sternberg presented a careful study of the pathology of these neoplasms New and Figi have reported 32 such patients observed at the Mayo Clinic, and Shaheen has recorded 58 such instances

The incidence is estimated at 0 05 per cent of all neoplasms of the head and neck The patients—all pubescent males—are usually in their teens

ETIOLOGY

Martin *et al* call attention to the following sex-endocrine factors which they consider of etiologic significance

1 The disorder was limited to young males

2 These patients in most instances gave the clinical impression of under-sexual development, both physically and emotionally

3 In spite of roentgen-ray therapy the tumor significantly regressed only after secondary sex characteristics were developed fully, there was one exception in the 29 cases represented

4 In two instances in which puberty was hastened by the administration of androgens, roentgen-radiation appeared to induce a more ready regression of the tumor *

PATHOLOGIC ANATOMY

The tumor has a pseudocapsule of atrophic nasal mucosa which often becomes ulcerated and bleeds violently (Fig 105) The color, pink or red, depends on the vascularity of the lesion Infection changes the texture of the neoplasm from smooth and firm to edematous and friable The histologic elements are angioblastic and fibroblastic in variable proportions, the neoplasms in younger subjects are usually richer in vascular tissue, even resembling cavernomas, but as they mature, there is an

* H Martin, H. E Ehrlich, and J C Abels Juvenile Nasopharyngeal Angiofibroma, Ann Surg, Vol 127, p 513, 1948

increasing paucity of blood vessels and a conversion to a more fibromatous structure. Vascular obliteration occurs from thrombotic obliteration of the lumen and from compression of the stoma. Degenerative changes in the vessel walls occur.

As the tumor grows expansively it may envelope mucous glands, nerves, bone, etc. There are structures which have been encompassed by the growing neoplasm but are not neoplastic constituents. The true angiofibroma of this location apparently does not undergo malignant changes.

SYMPTOMATOLOGY

The signs and symptoms in the usual order of their appearance have been nasal obstruction, recurrent epistaxis, progressive deformities of the face, palate and throat (frog face), rhinolalia, and anosmia (Fig. 106). The hemorrhages from nose and nasopharynx may be so severe as to require tamponage, which is unfortunate because this temporizing treatment is often followed by more severe bleeding, sepsis, and profound anemia. From its broad base the tumor may expand to project through the anterior nares, below the soft palate, into the maxillary antrum and cheek, and through the orbital floor to cause unilateral exophthalmos.

TREATMENT

A biopsy should antedate treatment and it should be borne in mind that the tumor is benign and tends to regress spontaneously with full sexual maturity. The following plan of treatment is a summation of that outlined by Martin, Ehrlich, and Abels.

1. Bilateral ligation of external carotid arteries to control recurrent epistaxis.

2. Administration of testosterone to accelerate sexual maturation. They discovered that hormone therapy alone was insufficient. (This principle was applied in reverse by Soskin and Bernheimer who induced mucosal hyperemia in patients with atrophic rhinitis by the administration of estrogens.)



Fig. 105. Surface appearance of nasopharyngeal angiofibroma. The neoplasm has no true capsule. In this photomicrograph intact mucosa may be seen stretched over the tumor forming a pseudocapsule. (*Courtesy* H. Martin, H. E. Ehrlich, and J. C. Abels and Ann. Surg. *127*:513, 1948. J. B. Lippincott Company.)

3. Radiation therapy to cause regression of the angiomatous portion of the tumor, to control dangerous recurrent hemorrhages, and to retard the growth of the lesion. X-ray therapy in fractionated doses through small circular ports (bilateral nasomaxillary and intraoral palatal) may be supplemented by interstitial irradiation in the form of gold radon seeds (5-6 mc.) repeated once or



FIG 106 Facial deformity in nasopharyngeal angiofibroma (*Left*) Marked facial deformity may be produced by a bulky nasopharyngeal angiofibroma as the mass grows outward, compressing the antrum and pushing the soft parts of the cheek ahead of it Removal of this tumor necessitated resection of the anterior wall of the maxilla and corresponding alveolus after reflecting a cheek flap (*Right*) Postoperative photograph (*Courtesy,* H Martin, H E Ehrlich, and J C Abels and Ann Surg *127* 513, 1948, J B Lippincott Company)

twice at monthly intervals It should be remembered that this is a benign neoplasm, and great care should be exercised to avoid overadministration of irradiation

4. Surgical removal of the major bulk of the tumor, after good exposure, by means of a reflected cheek flap (Weber-Ferguson incision) or through the anterior alveolar process The broad base of attachment can be removed in its entirety This technic is particularly indicated for tumors which may hemorrhage extensively, and it may thus become a life-saving procedure

Barring deaths from the complications previously listed, all patients with nasopharyngeal angiofibroma should survive and remain free of recurrence In a series of 25 cases reported by Sternberg, there were 2 deaths due to complications from the angiofibroma. One patient died of a brain abscess and another from aspiration pneumonia

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DESMOID TUMORS*

The desmoid tumor has been firmly established as an anatomic and clinical entity The morphology of this neoplasm was first described by Macfarlane in 1832

The term *desmoid* (band appearance) was introduced by Mueller in

* In collaboration with Harry E Ehrlich

1838 because he was impressed with the dense, tendonlike consistence of the tumor

During the past fifty years comprehensive reports on tumors of the desmoid group have been published by Ledderhose Pfeiffer Powers Stone, von Klot Stewart and Mouat, and others

DEFINITION

Desmoid tumors are essentially hard fibromas situated in the flat muscles of the anterior abdominal wall, characteristically occurring in young parous women and frequently recurring following limited surgical removal More specifically the tumor is an unencapsulated, infiltrating fibroma of fascial or aponeurotic origin, with a microscopic appearance which varies from that of an acellular fibroma to that of a cellular low-grade fibrosarcoma. Similar growths located in skeletal muscle other than in the abdominal wall have been included in the desmoid group by certain authors particularly by Nicholas Mason, Waugh, and Pearman and Mayo This extends the definition of Mueller to include all fibromas infiltrating muscle and non metastasizing fibrosarcomas of the fascia tendon-aponeurotic type

INCIDENCE

Desmoid tumors are rare This can be judged by the fact that Cabot encountered only 3 such tumors in 4,876 tumor cases Andrews reported 2 cases among several thousand laparotomies Stone described 5 cases in a series of 21 000 surgical patients at Johns Hopkins Hospital and Guerlt s collection of 16 637 tumor cases from the Vienna hospitals contained only 0 13 per cent of desmoid tumors

From 1917 to 1943 inclusive, 17 desmoid tumors of the abdominal wall were encountered at the Memorial Hospital and during this period, 50,346 cases of neoplastic disease were admitted to the hospital (first admissions) This made a gross hospital incidence of 0 03 per cent In this series desmoid tumors comprise 3.5 per cent of all tumefactions 4 2 per cent of all true neoplasms 5.5 per cent of all primary tumors, and 7 0 per cent of all benign tumors in the anterior abdominal wall.

ETIOLOGY

No definite common causative factor for this tumor could be determined In no case could a definite history of trauma be elicited, nor were there any evidences of neurofibromatosis, keloidal tendencies or any allied manifestations of an over development of connective tissue Although desmoid tumors which arise in laparotomy scars have been reported by Andrews Danforth Nichols and Bessesen no such instance occurred in our series

The one factor that appears to be of etiologic significance in the causation of desmoid tumors is pregnancy With but one exception all the female patients in this series (15) had had a recent gestation These patients had borne at least one child, and in the majority of cases the tumor was first noted during pregnancy or within the first year following delivery (Table 32)

The hypothesis has been advanced that the tumor in female patients may arise on the basis of an unhealed injury to the abdominal wall sustained during the period of pregnancy or parturition but when it is encountered in infants children and nulliparous women, as well as in laparotomy scars, it suggests an anatomic predisposition to tumor growth in this region The injury during pregnancy conceivably could be the tension or spreading of fascial or aponeurotic fibers which occurs in somewhat the same fashion as the more superficial striae gravidarum are produced.

Geschickter has assayed various fibrous tumors for estrogens and gonadotropic substance He found 13 000 rat



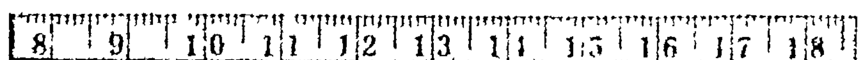


FIG 107 Bisection of a circumscribed type of desmoid tumor Muscle tissue is attached to both poles of the tumor (Pack and Ehrlich, Surg Gynec & Obst 79 177, 1944 *Courtesy*, Surgery, Gynecology and Obstetrics)

units of gonadotropic substance per kilogram of tumor in a desmoid tumor of the abdominal wall but did not find any estrogen, he suggested, therefore, that the neoplasm has the power to concentrate gonadotropic substance Aschheim-Zondek tests or their equivalents have apparently never been carried out in patients who harbor desmoid tumors There are no further data available to reveal a more specific sex-endocrine relationship, and there is no case of desmoma in adults on record which has been treated by the administration of sex hormones, although we have experimentally and unsuccessfully attempted it in children

PATHOLOGIC ANATOMY OF DESMOMAS

Gross Pathologic Anatomy

As its name implies, the desmoid tumor is a dense, hard, fibrous growth which may be circumscribed (Fig 107) or diffusely infiltrating in type In either case it characteristically compresses and invades muscle It is almost always solitary and unilateral If the tumor is circumscribed, the shape is usually round or oval, and the long axis of the mass is parallel to the long axis of the muscle involved This peculiarity can be explained by the well-known tendency of tumors to grow in the line of least resistance The circumscribed type contains no true capsule The diffusely infiltrating type may extend into the flat muscles for a considerable distance, occasionally producing multiple tumors and rarely involving the abdominal wall bilaterally No tumor in this series was attached by a pedicle Generally, neither the anatomic type nor the size of the tumor was in any way related to its cellular structure The specimens varied from 5 to 20 cm in greatest diameter The largest tumor recorded in the literature, by Rokitansky, weighed 17 kg The tumor

is usually white but may be yellow or grey The surface is smooth or nodular and a crisp grating sound is produced when the mass is cut.

Although no true "bone pedicle" was demonstrated in any of the patients in this series, these tumors, as their counter part in striated muscle outside of the abdominal wall show a tendency to infiltrate into joints and to become ad herent to bone. In Pfeiffer's series, 16 per cent of the cases showed periosteal attachment, while in this series the tu mors were found to extend to the peri osteum of the pelvic bones in 41 per cent of the patients They were most usually attached to the inner surface of the iliac crest. Occasionally a growth was densely adherent to the transverse processes of the adjacent vertebrae or to Poupart's ligament. Not infrequently the parietal peritoneum becomes involved by the tu mor but only rarely does the growth penetrate into the peritoneal cavity Those desmoid tumors which have their origin in the posterior rectus sheath or in the transversalis fascia are the growths most liable to become firmly attached to the parietal peritoneum It is generally stated that desmoid tumors do not ex tend through the subcutaneous tissues to involve the skin.

The vascularity of desmoid tumors is generally poor, but, unlike other tumors with a scant blood supply, these neo- plasms do not undergo necrosis or lique- faction and this may be attributed to the essentially fibrous nature of the tu mor A desmoid tumor which has under gone extensive malignant transformation is usually soft in consistency and rela tively vascular and is the one most liable to produce cutaneous ulceration.

Histopathology and Histogenesis

The *microscopic* appearance of the desmoid tumor is that of a fibroma plus the presence of bundles of striated mus cle fibers in various stages of atrophy

The histologic picture may vary f that of an acellular fibroma to that cellular low grade fibrosarcoma often the structure strongly resem that of a neurofibroma because of presence of intertwining fibrils and c but microscopic study following spe silver staining reveals that the ne matous pattern is produced by fi blasts and their interlacing fibrils ra than by fibroglial fibrils

It is not uncommon to encounter of fibrosarcomatous and myxosarco



Fig. 108 A desmoid tumor which undergone malignant transformation App ance is that of a low grade fibrosarcoma. compressed muscle bundles in the lower ri hand corner This tumor was clinically ben (Pack and Ehrlich, Surg. Gynec. & Obst. 177 1944 *Courtesy* Surgery Gynecology Obstetrics.)

tous transformation in this group of neoplasms, and rarely a tumor may have the appearance of a low-grade fibrosarcoma throughout It is significant that among cases previously reported malignant transformation was particularly common in males Of the three cases of malignant transformation in the present series, two occurred in males and one in a female patient There is no relation between the size of the tumor and the incidence of malignancy, nor can a definite conclusion be drawn either from an analysis of this series of cases or from a survey of the literature on the relation of the duration of the tumor to the incidence of malignant transformation.

The histogenesis of desmoid tumors has been established since the days of Mueller, *i e*, the neoplasm arises from the fibroblasts of the deep fascial and aponeurotic structures of the anterior abdominal wall Although Ewing has called attention to the strong but superficial resemblance of these tumors to neurofibromas, there is no evidence to support any histogenetic relation between these two neoplasms.

Desmoid Tumors Versus Fibromas

The desmoid tumor differs from the ordinary fibroma in that it is often unencapsulated, possesses infiltrative tendencies, and attains considerable size Characteristically, the desmoid tumor always compresses, invades, and destroys muscle The usual encapsulated fibroma is never aggressive Tumors of the desmoid group occasionally contain foci of sarcomatous transformation While simple fibromas are largely situated subcutaneously, desmoid tumors invariably have their origin in the deep fascial and aponeurotic structures of the anterior abdominal wall Desmoid tumors commonly recur following limited surgical excision, while fibromas show less likelihood to reappear

CLINICAL COURSE AND DIAGNOSIS OF DESMOID TUMORS

There are no special symptoms characteristic of desmoid tumors The mass is usually first noted by the patient or discovered during routine abdominal examination Pain, although infrequent, is dull and centered over the tumor site The tumor is always slow-growing and of relatively long duration. It occurs most often in gravid or parous women, making its appearance during gestation or, more usually, within the first year following childbirth. If noted during pregnancy, the mass does not regress after delivery, on the contrary, growth is progressive

In the majority of our patients, the neoplasm was located within the right lower abdominal quadrant and only rarely crossed the midline The significance of this topographic distribution, although of diagnostic import, is difficult of evaluation Inasmuch as the tumor is deeply situated and only rarely shows a tendency to extend to the subcutaneous tissues and skin, the mass may have reached considerable proportions when first seen by the examiner. The average size at the time of admission is 8 by 10 cm in the greatest diameter, The tumor is usually fixed, nontender, and solitary Since the mass is located intramurally, Bouchacourt's sign may be demonstrated in almost every case. This may be revealed by having the patient contract the muscles of the anterior abdominal wall by flexing the head, following this maneuver, an intraperitoneal mass can no longer be palpated or only very slightly, but an intramural mass becomes more prominent Occasionally, it is difficult to determine by physical examination alone whether the tumor is situated in the abdominal wall, peritoneal cavity, or retroperitoneal space Under such circumstances surgical exploration must be resorted to before the exact location of

the neoplasm can be established. When ever a deep-seated tumor of the lower anterior abdominal wall is encountered in a young parous female especially if it is related to a recent gestation, a presumptive diagnosis of desmoid tumor is justified.

Aspiration biopsy proved of no positive value as a *diagnostic measure in this* group of tumors The procedure was performed in five cases and repeated in one case, with negative reports in all. Because of the essentially fibrous nature of the neoplasm, one would not expect it to yield tissue on aspiration which would be sufficiently characteristic for microscopic identification This diagnostic aid should not be omitted, however even when the possibility of desmoid tumor is being entertained, for one might be dealing with a neoplasm of which the histologic structure can be determined by aspiration biopsy and which might not best be treated by primary radical surgical excision *viz.* liposarcoma, lymphosarcoma or metastatic carcinoma.

Growth and Recurrence Rate

Growth generally is progressive, and if of sufficient duration (from 7 to 10 years) the neoplasm may reach huge proportions involve the entire abdominal wall, and penetrate into the retroperitoneal space or even into the abdominal cavity and pelvis These tumors may become adherent to the umbilicus Poupart's ligament, or the periosteum of the pelvic bones They sometimes undergo malignant transformation into low grade fibrosarcoma, but they never involve the regional lymph nodes or produce distant metastases The incidence of malignant transformation is particularly high in male patients One of the striking clinical characteristics of desmoid tumors is their tendency to recur following local surgical excision One-fourth of our patients gave a history of from one to six recurrences *following* initial surgical removal In this series recurrences were especially frequent during subsequent pregnancies and following subsequent childbirths

TREATMENT

Surgical Treatment

The treatment of choice for operable desmoid tumors is radical surgical excision. This was advocated as long ago as 1899 by Bouffleur Successful resection of the parietal peritoneum for desmoid tumors was first performed by Saenger in 1884

Adequate surgical management of the neoplasm may necessitate resection of a considerable portion of the abdominal musculature, underlying parietal peritoneum, periosteum of the pelvic bones and the adjacent vertebral ligaments, or the splitting of Poupart's ligament. Although the neoplasm is essentially benign, local recurrences are frequent, so that excision must be wide and complete.

The parietal *peritoneum is sufficiently* elastic so that closure following peritoneal resection is not technically difficult. Large fascial defects may be adequately closed by suture in a transverse direction (as in the Mayo repair for umbilical hernia) or even by use of fascial transplants or tantalum mesh implants The fascia should always be overlapped to prevent postoperative hernia The elasticity and frequent redundancy of the anterior abdominal wall, especially in parous women, facilitate considerable stretching so that closure of large defects *may be effected without* undue tension It may occasionally become necessary (especially in male patients) to resort to a sliding muscle graft *brought over* from the flank.

Inasmuch as adequate surgical treatment of desmoid tumors usually results

TABLE 32 DESMOID TUMORS OF THE ABDOMINAL WALL: A TABULATION OF CLINICAL AND PATHOLOGIC DATA
(Authors' Series)

Case Number	*Sex and Age*	*Duration of Tumor*	*Size of Tumor*	*Number of Pregnancies*	*Number of Childbirths*	*Postpartum Interval before Appearance of Tumor*	*Muscles Involved*	*Topographical Distribution*	*Osseous Attachment*	*Peritoneal Involvement*	*Recurrences Prior to Admission*	*Recurrences after Excision at Memorial Hospital*	*Recurrences Following Pregnancy*	*Malignant Transformation*	*Response to Irradiation (Recurrences)*	*Follow-up Period (Yr)*	*End Results*
1 A B	F 23	7 yr	Entire abdominal wall	3	3	1 yr	Recti abdominis	Lower abdominal wall *Bilateral*	+	+	2	1	+	+	±	3	Tumor controlled, then patient lost to observation
2 I B	F 25	1 mo	10 cm	2	2	4 mo	External oblique	Right lower abdominal quadrant	0	+	0	2	0	0	+	10	Controlled
3 F H	F 30	3 mo	5 cm	2	2	3 mo	Internal oblique	Right lower abdominal quadrant	0	0	0	1	+	0	+	16	Cured
4 F L	F 32	5 yr	19 cm	1	1	5 yr	Internal oblique	Right lower abdominal quadrant	+	+	0	0	0	0	–	4	Cured
5 A R	F 29	1 yr	10 cm	4	4	3 yr	Latissimus dorsi	Right lower abdominal quadrant	0	0	0	0	0	0	–	16	Cured
6 M H	F 34	1 yr	12 cm	2	1	7 mo	Rectus abdominis	Right flank	+	0	0	0	0	0	–	7	Cured
7 M G	F 30	3 mo	8 cm	1	1	1 yr	Transversalis	Left lower abdominal quadrant	0	0	0	0	0	0	–	12	Cured
8 I M	M 44	4 yr	5 cm.				Rectus abdominis	Right upper abdominal quadrant	0	0	2	0		+	0	9	Cured

sue appeared to replace muscle in
ne areas"

This historical review totals 16 cases
desmomas arising in the abdominal
ll of children, but some of them are
ry poorly documented, and in some
e histologic diagnosis may be consid
ed doubtful. The authors have added
ree cases occurring in their experience
Table 33)

CASE REPORT NO 7

J B an 8-year-old white boy was first
lmitted on November 16 1944 with the
mplaint of a recurrent tumor in the ab-
minal wall of one month's duration The
mor originated above the left groin at the
e of 4 years. There had been no trauma
this region Surgical excision was per
rmed elsewhere in June 1942. A diagnosis
desmoid tumor was made and postop-
ative low voltage roentgen ray therapy
as given According to information re-
eived, a dose of 450 r with a 130 kv
achine was given in two treatments six
ays apart.

One year later when the patient was 7
ears old, the mass reappeared, and on June
4 1943 it was again "removed widely with
portion of the external oblique fascia " and
e defect repaired with fascia lata The gross
escription was "an ovoid tumor 5 × 3.5 × 2
m in size which on sectioning was light
ray and fascicular and presented a distinct
apsule" It was classified as a desmoid
umor In the postoperative course the pa
ient was given a series of high voltage
oentgen ray treatments receiving 242 r on
lternate days between August 3 and 16
943

(A maternal aunt of this patient had had
desmoid tumor of the abdominal wall re-
noved We verified this familial history by
orrespondence with the hospital and
urgeon.)

Physical Examination

The physical examination showed an ap-
parently normal 8-year-old boy In the left
ower abdominal quadrant, beneath an
bliquely placed scar was a mass measuring
7 × 3 cm It was multilobular freely mova
ble, and involved the entire thickness of the
abdominal wall It was definitely not con-
nected to the ileum. There was a café-au
lait spot on the abdominal skin, and, al
though it was believed that this tumor was
a desmoid, the possibility of a plexiform
neurofibroma was considered because of this
pigmentation

The laboratory data showed a mild sec-
ondary anemia with a hemoglobin of 73 per
cent (Sahli) red-cell count, 3 700 000 and
white-cell count, 4300 with a normal differ
ential distribution. Frank Foote reviewed
the submitted microscopic slides and stated
that the tumor was composed of diffuse
hyaline fibrous tissue which was so acellular
that it was hardly characteristic of either a
desmoid or a plexiform neurofibroma

Treatment

On November 17 1944 a wide surgical
excision was performed, taking the full
thickness of the abdominal wall and excising
normal tissue well beyond the palpable mar
gins of the tumor A layer closure was done
using chromicized catgut in the peritoneum
but interrupted silk in the rest of the wound.

Pathologic Report

The specimen (Fig 109) consisted of an
irregular mass 9 × 4 × 3 cm surrounded
by normal appearing muscle and presenting
glistening peritoneum on one surface The
cut surface showed hard, smooth, pinkish
white tissue which on microscopic study
was considered characteristic of desmoid
tumor (Fig 110)

Postoperative Course

The wound apparently healed per pri-
mam but six months later a mass was pal
pable in the lower terminus of the scar and
on the patient's admission to the hospital, a
mass measuring 7 × 3 cm. was palpable This
tumor was widely excised on June 11 1945
and a layer closure was effected with diffi
culty This specimen showed a portion of
the abdominal wall removed in its entire
thickness measuring 13 0 × 3 0 × 2 8 cm

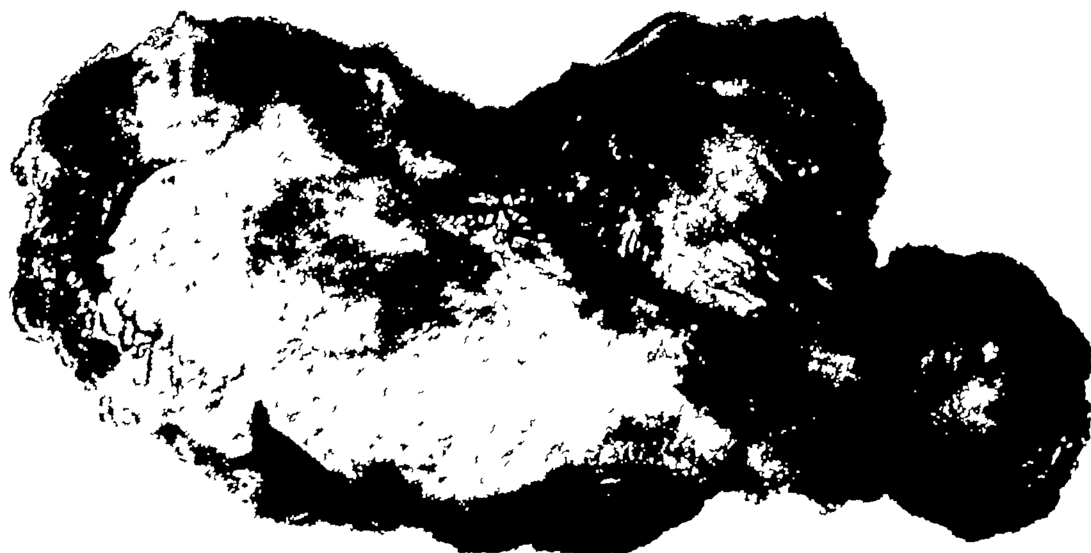


Fig 109 Gross pathologic specimen of desmoid tumor at the time of the third excision The neoplasm has become invasive (Case report No 7) (Figs 109–118 from Booher and Pack, Cancer *4* 1052, 1951)

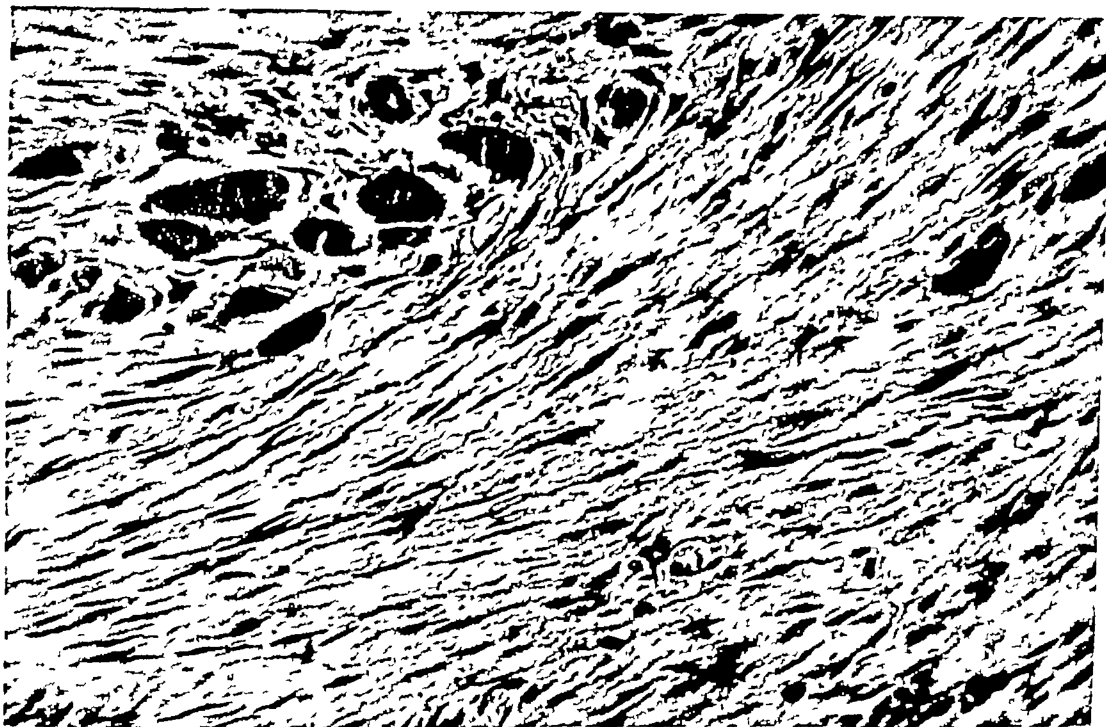


Fig 110 Photomicrograph of Fig 109 showing engulfed striated muscle cells in the substance of the desmoid tumor (× 200)

The tumor was covered by normal skin but extended through the full thickness of the wall and was adherent to the peritoneum The tumor, measuring 7 0 × 3 0 × 2 8 cm, appeared to be well circumscribed and encapsulated The cut surface presented interlacing bundles of connective tissue, greyish pink in color, but with a fairly homogeneous surface In several sites the tun ed to within 1 to 2 mm of the c specimen The microscopic c was "desmoid tumor"

The patient was then given roentgen ray therapy by using a 250,000 volt machine, a, 1 5 mm copper tion, and 5 with a portal cm, givi ctions in dail ment fro to 22, until dose of 2(given By e tion on S 1945, all had subsid as no evi tumor

At two-m aminati recurrent neo ent unt 1946, when r d al entire scar B ulty



Fig. 111 Desmoma in childhood Photograph showing the extent of recurrent tumor 7 years after the first excision (Case report No 7)

previous closure, it was not felt that surgical excision could be done and closure still effected. Illustrative of the extent of the previous excisions was the fact that the interspinous measurement was 19 cm and the navel was only 3 cm. from the left anterior superior iliac spine High-voltage roentgen ray therapy was again started with the same factors 300 r fractions were given alternately each day to a left lower-abdominal and a left flank portal until 1800 r had been delivered to each field on June 25 1946 Marked regression followed, but, ten weeks following this treatment, 1500 r by using the same factors, was delivered to nodules persisting at the upper and lower poles of the scar In December 1946 the tumor was again growing actively and masses at the upper pole of the incision measured 2.5 × 3.5 cm and at the lower pole 4 × 5 cm Beginning December 21 with a portal 7 × 9 cm over the lower pole and a portal 8 × 10 cm above using 300 r fractions and with the remaining factors identical 1200 r was delivered to each of these fields By March 1947 these two recurrent tumors seemed to be under control

By July 1947 the mass at the upper pole of the wound began to extend deeply into the left flank Surgical excision of this was as impossible as before and tolerance for additional roentgen ray therapy was limited. However on August 25 1947 irradiation was started over the left flank, giving 250 r daily until 2000 r had been given to a large portal with the factors previously used In November 1947 1000 r was delivered to the lower abdominal wall At the completion of this treatment some growth restraint was apparent

In January 1948 daily Teropterin injections were instituted, the dose being increased gradually to 30 mg daily by mid February and in March after two and one-half months treatment, Teropterin was discontinued with no apparent change in the tumor Theodore Miller then planned a course of interstitial radiation for the most active portions of the tumor and, between March 25 and June 3 injected gold filtered radon seeds to deliver a total dose of 37 mc. destroyed. This seemed to exert little growth restraint

Because of suggestive evidence indicating some control of fibrous dysplasias with vitamin E 100 mg doses of a mixture of alpha tocopherols were instituted by Miller This also failed and the tumor grew rapidly

Because of the rather striking observation of Martin Ehrlich and Abels concerning the sex-endocrine factors in relationship to the etiology of juvenile nasopharyngeal

fibromas, in which experience these tumors regressed only after secondary sex factors were developed fully either by the natural occurrence of puberty or by the use of the male sex hormone, it was thought that, if a deficiency of androgen activity could be a factor in the production of these tumors, it might be a good therapeutic consideration in this case Accordingly, Miller prescribed intramuscular testosterone propionate in 25 mg doses twice weekly Signs of puberty that were just appearing were accelerated, but no evidence of growth inhibition was shown by the tumor

A superficial ulceration had been a problem for some time (Fig 111). The ulcerating, fungating tumor eventually became so large and daily care so difficult that it was decided to temporize by partial cautery excision. Accordingly, on July 15, 1949, all the protuberant tumor was removed by a combination of sharp dissection and actual cautery After the excision a mixture of 50 per cent zinc chloride solution and charcoal in flour was applied over the entire area The result was remarkable, and the patient was discharged from the hospital on the fifth postoperative day with a comparatively clean wound

The pathologic report described a large, nodular mass measuring 20 × 16 × 11 cm, covered by skin that showed marked lichenification, coarse trabeculations, and numerous areas of hyperkeratosis with scaling and desquamation The tissue was moderately firm, homogeneous, pale, tannish grey, and somewhat edematous and contained occasional dilated veins The tissue lacked any semblance of capsule. The microscopic diagnosis was "desmoid tumor."

Healing proceeded, and by December 13, 1949 (Fig 112), the greater part of the wound had epithelialized, but troublesome hemorrhage occurred on one occasion at this time and necessitated hospitalization for packing and pressure dressings.

Intestinal obstruction required hospital admission on January 22, 1950, it was relieved by conservative measures

Because of the remarkable report of the effect of cortisone and adrenocorticotropic hormone (ACTH) in the reduction of stiffness and pain in rheumatoid arthritis and because of reduction in swelling in articular connective tissues, it appeared logical to use either one of these agents in dealing with this neoplastic overgrowth of connective tissue

This boy was admitted to Flower-Fifth Avenue Hospital and for a period of six



Fig 112 Desmoma Photograph showing the extent of epithelization over the tumor following removal by cautery (Case report No. 7)

weeks received a carefully controlled series of treatments with ACTH Irving Ariel su pervised the metabolic studies and adminis tration of this agent.

There was diffuse softening of the tumor but no dramatic response. He then received 10 mg of methyltestosterone by mouth daily which resulted in slight water reten tion, which was in turn corrected by small doses of Mercuhydrin





FIG. 113. Photograph showing a desmoid tumor at the time of the first excision, with glistening tumor apparent beneath the peritoneal surface. (Case report No 8)

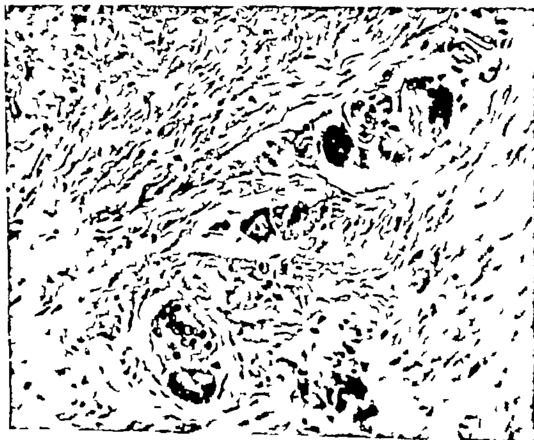


FIG. 114. Photomicrograph of Fig 113 showing a not very cellular desmoid tumor with giant-cell formation. (× 185)

On August 24, 1950, he developed diarrhea, projectile vomiting, excruciating right-lower-quadrant pain, and severe thirst All findings indicated a subacute intestinal obstruction for which the usual measures were instituted, though the child could not cooperate with the Levine tube for suction There had been a right-sided pleural effusion developing, which yielded 1200 cc of chylous opalescent fluid and which on culture showed a growth of *Aerobacter aerogenes* The child's condition gradually declined, and on September 4, 1950, his twelfth hospital day, he died

The autopsy showed that the long-standing growth of the tumor in the right flank had infiltrated through the left side of the posterior abdominal wall and into the base of the mesentery and had completely replaced it so that the small bowel appeared to be suspended from the tumor itself There was a generalized peritonitis, but no site of perforation of an abdominal viscus could be determined Incidental findings were a right-sided empyema and a very recent perforation of the thoracic esophagus No evidence of remote metastases was found

CASE REPORT NO 8

C G, a 2-year-old girl, was admitted to the hospital for treatment of a mass in the lower left abdominal wall When the child was 1 year old, her parents noted a mass of the abdominal wall which was locally excised 6 months later by her local doctor and diagnosed by Dr F W Stewart as desmoid tumor Re-exploration revealed a tumor adhering to the underlying parietal peritoneum This was widely excised

A second recurrence occurred 5 months later, and a wide dissection was again performed A third and fourth resection were subsequently performed 3 and 5 months later The child remains well, 5 years after the last local excision

CASE REPORT NO 9

H G was admitted to the hospital on February 2, 1950, for treatment of a desmoid tumor of the right abdominal wall

This 22-month-old white boy had always had good health In November, 1949, his mother discovered a firm subcutaneous mass, the size of a quarter, just above and to the right of his umbilicus She consulted her physician who advised observation for one month After one month, on January 2, 1950, an excision was performed in another hospital The pathologic report was given as a spindle-cell sarcoma Our review of this microscopic slide led to the diagnosis of desmoid tumor At that time a small, firm nodule was still palpable in the lower pole of the incision

Physical Examination

Physical examination revealed a well-developed, alert white male of 22 months Abdominal examination revealed an upper-right-abdominal scar in the rectus muscle measuring 7 cm in length, at the lower pole



Fig 115 Desmoid tumor Photomicrograph of the first recurrence showing a little more cellular fibroma than was apparent on the first excision (× 115) (Case report No 8)

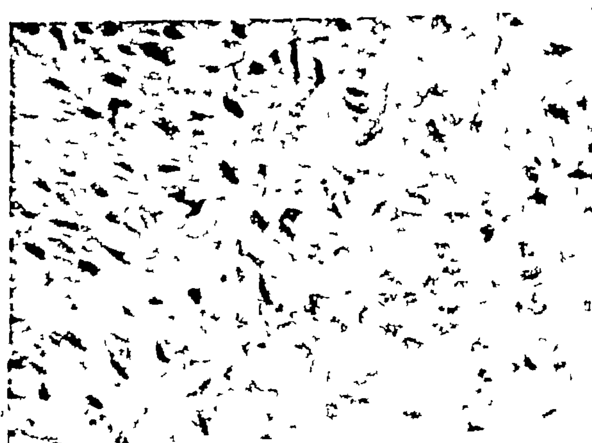


Fig 116 Desmoid tumor Higher magnification of Fig 115 showing the benign fibroma with comparative uniformity of structure (× 292) Patient remains free from evidence of tumor five years later

of which was a small nodular tumor The diagnosis was tentatively considered to be residual desmoid tumor

Treatment

On February 2 1950 a wide local excision of the tumefaction was done A block dissection of the skin, subcutaneous tissue and entire thickness of the abdominal wall was done opening the abdomen on the medial side of the previous scar Then with a guiding hand on the peritoneal surface the right lateral margin was excised to give an adequate margin of apparently normal tissue on all sides of the tumor The wound was closed in layers using 00 silk interrupted with vertical mattress sutures of black silk in the skin

Pathologic Report

The pathologic report described a mass of tissue consisting of a full thickness of the abdominal wall There was an ill-defined, firm mass measuring 2 × 1 cm that blended with the rectus abdominis muscle (Fig 117) There appeared to be a margin of normal muscle of about 1 cm on one side of the specimen and 3 cm on the other side Microscopic examination revealed the neoplasm to be a desmoid tumor (Fig 118)

The baby's subsequent course has been uneventful, and when seen March 1 1957 the wound was normally healed and soft There was no evidence of recurrence

In our series of three cases in children, a review by F W Stewart and Frank

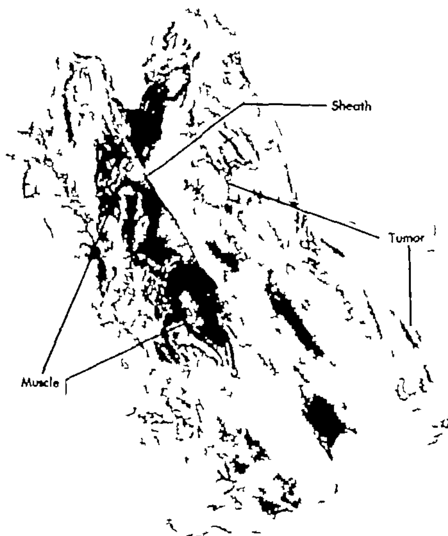


Fig 117 Desmoid tumor Sectional gross specimen of the first recurrence showing the origin from the posterior sheath of the rectus muscle (Case report No 9)

TABLE 33. REVIEW OF DESMOID TUMORS IN CHILDREN

Author	*Sex* *Age*	*History of Trauma*	*Duration*	*Site*	*Size*	*Histology*	*Treatment*	*Follow-up*
Temoin, 1893	Female 14 yr.	No	12 yr	Extending from false ribs to crural arch	1400 gm	"Fibrolipomatous"	Wide local excision	No recurrence in 2½ yr
Kramer, 1896	Female 24 mo	No	—	—	—	—	—	—
Kramer, 1896	Female 54 mo.	No	—	—	—	—	—	—
Sonnenschein, 1900	Female 18 mo	No	16 mo.	Left of umbilicus	Size of apple	Composed of "fibrous tissue"	Excision	—
Freudenstein	Male 12 yr	No	6 mo	—	—	Fibroma	Excision	—
Abels, 1902	Male 24 mo.	No	Congenital	—	Size of apple	Composed of fibrous tissue, slightly nucleated	Excision	—
Pfeiffer, 1904	Female 30 mo	No	Congenital	Superficial fascia of abdomen	—	None	Excision	—
Greig, 1915	Female 20 mo	No	12 mo	To the right and above umbilicus	1 in	—	Wide excision	None
Jemma, 1928	Female 12 mo	No	Congenital	Right lower quadrant	650 gm	Fibroma	Excision	No recurrence in 10 mo
Grenet & Mezard, 1931	Female 24 mo	No	Recent	—	65 gm	—	—	
Walters & Church, 1934	— 24 mo	No	—	—	—	Desmoid	Excision	—
Geschickter & Lewis 1935	Female 12 yr	No	—	—	—	Desmoid	Excision	—
Waugh, 1940	Male 60 mo	Yes	18 mo	Right upper abdomen	7 × 10 cm	Desmoid	Excision	—

Author	Sex Age	History of Trauma	Duration	Site	Size	Histology	Treatment	Follow-up
Ladd & Gross 1941	Female 21 mo	No	—	Central sub-umbilical	7 × 7 × 3.5 cm	Perineural fibroblastoma?	Excision	—
Sujov & Maggi 1942	Female 7 yr	No	4 mo	Left lower quadrant	—	Fibromyoma	Excision	No recurrence in 1 yr
Brockman, 1947	Female 1 mo	—	Congenital	Central sub-umbilical	15 × 8 cm.	Desmoid	Wide excision	Postoperative death
Ackerman, 1948	Male 11 yr	Surgical trauma (operative scar)	2 yr	In appendectomy scar	8.5 × 6 cm	Desmoid	Wide excision	—
Booher & Pack, 1950	Male 4 yr	No	4 yr	Left lower quadrant	9 × 4 × 3 cm.	Desmoid	Wide local excision	Fourth recurrence too extensive for excision patient died with disease 8 yr after first excision
Booher & Pack 1950	Female 2 yr	?	4 mo	Left lower quadrant	9 × 4 × 3 cm.	Desmoid	Wide excision	Excision of 3 recurrences within 28 mo, no evidence of disease at present
Booher & Pack, 1950	Male 22 mo	No	3 mo	Right upper quadrant	2 × 1 cm	Desmoid	Wide excision	No evidence of disease 7 yr

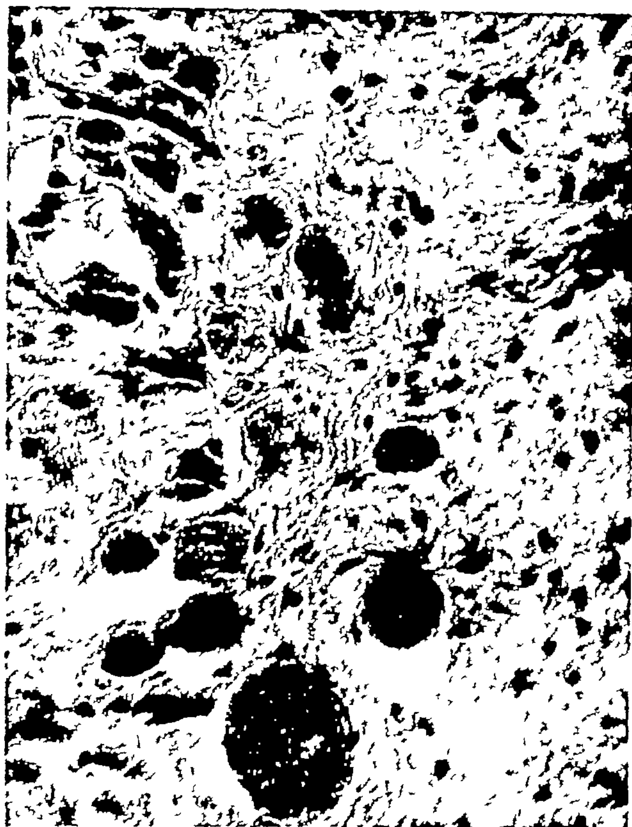


Fig 118 Desmoid tumor Photomicrograph of Fig 117 showing the fibroma engulfing striated muscle fibers (× 440)

Foote of all of the sections available from these tumors has led them to conclude that, on the basis of histologic structure alone, these neoplasms were not malignant On the basis of clinical course alone, two of these neoplasms would suggest that the ultimate end result would justify their classification in the group of malignant tumors because of their uncontrolled invasion In all respects they comply with the histologic and gross description for desmoid tumors, and we cannot conclude that they represent an inflammatory or metabolic fibroplastic diathesis These neoplasms, which in their earlier phases of excision have appeared to be completely excised (as determined by gross evidence of striated muscle entirely around the specimen and the excision of full thickness of the abdominal wall, with histologic evidence of complete excision), also have recurred, indicating that in these three cases occurring in otherwise normal children, bearing no evidence of altered hormonal status, all of the potentiality of local recurrence is present in these lesions as they occur in prepubescent ages Although hormonal assay of the tumors has not been possible and ketosteroid determinations have not been done, the otherwise grossly normal characteristics of these three patients would indicate that a normal hormonal titer must have obtained in each individual, and in these patients it would not seem necessary to postulate a factor relative to hormonal status as etiologic in this tumor process

These cases exemplify the observation of Wilson that every relatively cellular fibroma, no matter how casual its clinical or histologic appearance, should be considered malignant until its subsequent behavior is established If the surgeon is mindful of this, his first attack must be a radical excision of the growth without primary concern for the problem of closure of the wound

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DERMATOFIBROSARCOMA PROTUBERANS*

INTRODUCTION

Darier in 1924 described an unusual progressive and recurring tumor of the skin of fibromatous or fibrosarcomatous character One year later Hoffmann reported several similar cases and coined the neologism *dermatofibrosarcoma protuberans* The neoplasm is rare, but it must have been seen and treated, though unidentified, many years before its recognition as a tumor entity In earlier years at the Memorial Hospital, it was erroneously considered to be a dermal neurosarcoma of low-grade malignancy.

This chapter is based on a series of 39 such tumors confirmed by histologic study and collected during a 20-year period Almost all these patients were treated by the authors

Thirty patients have been constantly available for follow-up observations, but nine were lost for subsequent appraisal An analysis of these nine delinquent patients confirms the accepted opinion of good results following surgical treatment, *viz*, a 52-year-old man exhibited no recurrence when last seen 3 years after treatment, a 42-year-old man had no evidence of tumor when last seen 3 years after treatment, one patient died of ocular melanoma 8½ years after the dermatofibrosarcoma was excised, two men aged 20 and 42 years when last seen 2 years after treatment were without evidence of recurrence, an 87-year-old woman when last seen was without recurrence 1⅓ years following treatment, a 41-year-old woman was lost to observation within 6 months after therapy, one man refused secondary treatment for a tumor recurrent after a year, and there was one operative death of a 41-year-old man, presumably due to anesthesia

* In collaboration with Edward J Tabah

SYNONYMS

In a collective review of the literature, it is evident that these tumors identical in type and possessing a similar clinical picture, course, and microscopic appearance have been variously designated by the numerous authors interested in this neoplastic entity The following names have been given to this neoplasm (1) *dermatofibrosarcoma protuberans* (Hoffmann) (2) *sarcomatous tumors resembling keloid* (R. W Taylor) (3) *hypertrophic morphoea* (Sherwell) (4) *progressive recurring dermatofibroma* (Darier and Ferrand) (5) *fibrosarcomatous tumors with attenuated dermal surfaces* (Hertzler) (6) *sarcomatoid fibroma of the skin* (McMaster) and (7) *fibrosarcoma of the skin* (A. P Stout)

HISTORIC REVIEW

The earliest description of this disease was published in 1890 by R. W Taylor who described a nodular lobulated, intracutaneous tumor present for 15 years on the left shoulder of a 43-year-old man. The clinical and histologic description of the lesion corresponds exactly with the tumor under discussion. It was locally excised four times with recurrence following each procedure. The fifth attempt was a wide surgical excision following this extirpation the patient was lost to observation

Binkley has introduced a case report culled from the collection of the Central Bureau for the Study of Tumors This patient was first seen professionally in 1890 with a cutaneous nodule 1 cm. in diameter situated on the anterior abdominal wall It grew to a diameter of 15 cm before it was excised in 1896 From 1912 to 1928 the patient underwent four operations for successive recurrences He finally died of metastatic sarcoma on September 2, 1928 38 years subsequent to the known onset

Sherwell presented a patient before the New York Dermatological Society in 1890 with the tentative diagnosis of "hypertrophic morphoea."

In 1903 J C. Johnston reported the case of an indolent intracutaneous tumor of 20 years duration on the shoulder of a middle-aged man It was excised *in toto* There were *no metastases* The author concluded that it was a slowly growing fibroblastic tumor of low malignancy having a tendency to recur if incompletely excised. He advocated wide surgical excision A study of the clinical appearance microscopic pathology and course of this neoplasm establishes it as a definite example of dermatofibrosarcoma protuberans

Kuznitsky and Grabisch in 1921 published three case reports of these tumors originating on the chest wall.

It was not until Darier and Ferrand published their classic article on this subject in 1924 that this tumor finally became established as a clinicopathologic entity They reported four cases at that time and added a fifth one in the ensuing year In his original article Darier made the statement that these growths had a tendency to occur on the anterior abdominal wall, because in his original four patients the tumors were found either close to the umbilicus or adjacent to the groin It has since been shown that, although the abdominal wall is one of the favorite sites for occurrence it is by no means the only one, and indeed it has developed practically everywhere on the body Darier quoted only a single bibliographic reference in which a similar tumor was described, namely by Professor Unna in his book *Histopathology of Skin Diseases* (1894) the location in this instance being juxta umbilical Darier perhaps in his enthusiasm to announce his independent discovery and because of his mistaken belief that these tumors arose primarily from the abdominal wall, neglected to study the references to more or less

identical neoplasms occurring on other parts of the body His thesis was otherwise thorough and authoritative, in fact, the neoplasm was subsequently referred to as Darier's recurring fibroma of the skin

Hoffmann in 1925 published 3 cases from his own experience and suggested the term *lump-producing fibrosarcoma of the skin*, or *dermatofibrosarcoma protuberans* Hoffmann gave priority to Coenen who in 1909 reported 2 dermal fibrosarcomas In his article Hoffmann made a detailed bibliographic study of this neoplastic disease Including his three patients, Hoffmann summarized a total of 15 published case reports fulfilling the criteria which he considered pathognomonic of this condition He included 3 case reports of Kartscher and 3 of Pfeiffer as typical examples of dermatofibrosarcoma protuberans, although those authors considered their reported neoplasms to be variants of desmoid tumors and were of the opinion that they arose from the superficial fascia and not from the skin However, the tumors in each of these 6 cases were said to have remained confined to the skin and subcutaneous tissues and were freely movable on their undersurfaces

Following the publications of Darier and Hoffmann, the recognition of this tumor as a specific neoplastic entity was generally accepted Pathologists as a whole did not classify it within the group of desmomas, fibromas, or fibrosarcomas originating from fascia, muscle, or tendon sheaths

ETIOLOGY

The following paragraphs present theories and evidence as to the histogenesis of dermatofibrosarcoma protuberans

1 *Parasitic theory* Darier originally attributed the onset of the tumor to the supposed local action of some unknown parasite

2 *Traumatic origin* Traumas have frequently been mentioned as possibly influential in the production of this growth Persistent irritation by a button is mentioned by Hoffmann as a presumptive cause of the tumor which developed on the volar aspect of the wrist Begnis and Picena observed the development of dermatofibrosarcoma protuberans in the scar of a human bite on a male breast In Hoffmann's review of 39 cases collected from the literature and including his own case, trauma was alleged to have preceded the initial appearance of the tumor in 8 instances In our series of 39 patients, a history of injury to the site on which the tumor arose was given by 5 patients (13 per cent) On the basis of this percentage, the traumatic relationship would seem to be only coincidental It could have served to attract the patient's attention to a previously existing mass Again it could have served as a "trigger mechanism" in stimulating the neoplasm to appear in a person already predisposed to its development by a desmoplastic diathesis We concluded that injury as an etiologic factor played no significant role in our series of cases It could very well be that some of the remaining patients had long since forgotten any specific blow or injury to the affected area We shall cite the 5 examples of reputed trauma (1) A 55-year-old man sustained a hammer blow to the sacral region and developed the tumor after a few weeks (2) A 47-year-old man fell against a machine, injuring the pectoral region and the neoplasm appeared three months later (3) A 74-year-old woman, after an interval of 39 years, discovered the tumor growing in the scar of an abdominal operation (4) A 34-year-old professional boxer's tumor occurred on the right upper chest wall, the site of repeated bruises (5) A 15-year-old woman's growth was in the skin of the right upper abdominal wall, where she experienced pressure from her corset

3 *Hereditary influence* There was no evidence of familial occurrence

4. *Mammogenic theory* Kuznitsky entertained the hypothesis that these tumors were probably misplaced embryonic remnants of breast tissue his three cases occurred on the chest wall. The histologic appearance does not support this contention. More recently Binkley favored Kuznitsky's hypothesis He made a spot map of the body showing the locations of dermatofibrosarcoma protuberans in reported cases The majority of these lesions were situated on the anterior surface to the right or left of the midline, either adjacent to or on the mammary ridge It was his assumption therefore that these tumors arise from embryonic breast tissue along the mammary ridge It is difficult to reconcile this conception with the occurrence of these tumors on the wrist, penis, head, back, and lower extremities as shown in the regional distribution of our cases

5 *Neurogenic theory* In 1929 Mosto introduced his theory of the neurogenic origin, contending that these tumors developed from the supportive tissue of the nerves or from nerve tissue proper He designated these lesions as dermatoneuromas or dermatoschwannomas Undoubtedly the cellular structure in some regions does suggest the diagnosis of neurofibroma or neurilemmoma. However in the various case reports no mention is made of the tumor occurring within a nerve trunk or requiring anatomic dissection from a nerve. Special tissue stains have not substantiated the theory that these tumors originate in the sheath of Schwann. Finally, in no reported case has there been evidence of associated cutaneous neurofibromas or von Recklinghausen's disease either fully developed or *forme fruste*

6 *Angiomatous theory* Hoffmann suggested the possibility of derivation of these tumors from blood vessels, as he was impressed by the presence of enlarged, lacunar thin walled blood vessels. In many instances the blood vessels were represented only by a single layer of endothelial cells with the remainder of the wall being replaced by the fibrosarcomalike tissue. The possible relationship of this tumor to the sclerosing hemangiomas of Gross and Wolbach has been noted by several observers Some pathologists consider them to be one and the same lesion, and, indeed, under the microscope it may be impossible to differentiate between them. There are, however certain definite differences The sclerosing hemangiomas are said to occur chiefly on the extremities, whereas dermatofibrosarcoma is distributed more commonly on the trunk. In their incipiency both neoplasms may appear as firm, intracutaneous nodules, but the sclerosing hemangioma is usually single, measuring a few millimeters to a centimeter in diameter and is not characteristically reddened. The sclerosing hemangiomas are featured microscopically by the presence of large numbers of phagocytes containing hemosiderin and vacuolated foam cells filled with lipoid substances interspersed among many fine capillaries and the connective-tissue framework of the tumor A P Stout emphasizes the fact that the neoplasm known as dermatofibrosarcoma protuberans does not characteristically contain the large number of foam cells or phagocytic cells containing blood pigment and that when these cells are present, they are coincidental and not integrate portions of the tumor

7 *Fibroblastic theory* By the use of Masson's trichome or Mallory's connective tissue stain it now becomes practically certain that the *basic structure* of this neoplasm is the fibroblast or connective-tissue cell. The tumor essentially *must* be considered to be a fibromatous or fibrosarcomatous *tumor* similar histopathologically to the other desmoplastic tumors of divers types but distinguished clinically by its location appearance, and manner of growth



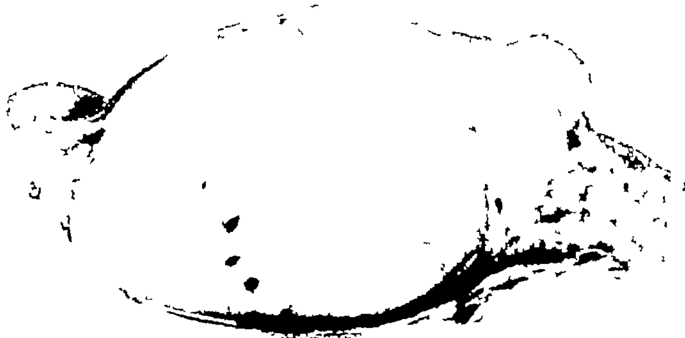




FIG 119 Gross specimens of two different dermatofibrosarcomas protuberans Note pseudoencapsulation and smooth, uniform texture (Pack and Tabah, A M A Arch Surg 62 391, 1951)

INCIDENCE OF DERMATOFIBROSARCOMA PROTUBERANS

This tumor is neither rare nor common The majority of published reports are based on only 1 to 6 personally treated lesions In 1926 Hertzler reported a total of 26 cases which he had accumulated from an experience with more than 5,000 tumors during a quarter of a century A P Stout collected 29 cases from the Laboratory of Surgical Pathology of Columbia University during the 40-year period 1907–1946 The 39 case reports from the Memorial Hospital constitute the largest series on record and are of more than average value because the tumors were treated on a single surgical service by the same surgical staff More than 50,000 patients with tumors enrolled in the institution during this period, therefore the incidence is slightly less than 0 1 per cent

PATHOLOGIC ANATOMY

GROSS ANATOMIC STRUCTURE

Dermatofibrosarcoma protuberans manifests itself on the skin surface as single or multiple nodules which are adherent to the overlying skin but which generally remain freely movable on the underlying fascia All were firmly attached to the skin, and the majority were confined to the dermis and subcutaneous tissue It develops usually from a single point of genesis, but multicentric origin has occurred The nodules may be sessile or pedunculated The latter conglomerate tumors have a corrugated or cobblestone appearance The epidermis is stretched thinly over the tumor but may be stripped from it The shiny translucent appearance of parts of the tumor may be due to myxomatous changes occasionally found In 32 of our 39 cases, the skin over the tumors was discolored, the color varying from a pale pink or red to a bluish red or purple, in 7 patients the superjacent skin was normal in color In time minute erosions of the skin occur, and later the exophytic tumor protrudes through the skin as a bleeding tomato-red mass The intact tumor is firm, but the fungating, infected edematous tumor may be soft and pulpy On cut section the lesion is ligneous and resistant and composed of a glistening greyish-white homogenous tissue which may be red and hemorrhagic at its core The appearance of encapsulation is due to a condensation of fibrous tumor tissue

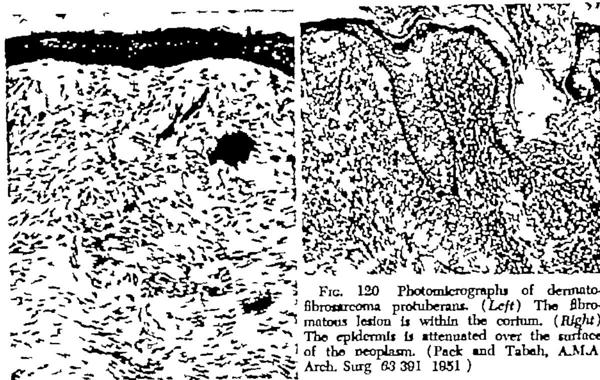


FIG. 120 Photomicrographs of dermatofibrosarcoma protuberans. (*Left*) The fibromatous lesion is within the corium. (*Right*) The epidermis is attenuated over the surface of the neoplasm. (Pack and Tabah, A.M.A Arch. Surg 63 391 1951)

at the periphery The growth separates easily from the fascia as a rule, because it seldom invades the subjacent fascia or muscle The neoplasm infiltrates on a horizontal plane through the corium and subcutaneous fat.

The proclivity of the tumor to extend in fine linear projections well beyond the apparent margins is responsible no doubt, for the common surgical error of too limited, conservative excision and subsequent regrowth of residual tumor Kuznitsky reported one case wherein the lesion had infiltrated the pectoralis major muscle. In our series of 39 cases there were only 5 instances in which the underlying fascia and muscle were infiltrated by the dermatofibrosarcoma protuberans These unusual case reports may be summarized (1) an 87 year-old woman in whom the recurrent tumor invaded muscles of the arm (2) a 45-year old woman in whom the tumor invaded the anterior rectus sheath (3) a 35-year old man in whom the tumor invaded the anterior rectus sheath (4) a 42 year-old man in whom the recurrent tumor invaded the fascia over the latissimus dorsi muscle and (5) a 63-year-old woman in whom the recurrent tumor invaded the deep epigastric fascia. Invasion of muscle and fascia by recurrent dermatofibrosarcoma is readily understood The slow growth of the tumor probably explains why the fascia and muscles are not invaded sooner, but as with all neoplasms possessing infiltrating capabilities it would appear that with sufficient time the adjacent structures would be ultimately invaded in all cases

HISTOLOGIC STRUCTURE

The microscopic appearance of the dermatofibrosarcoma protuberans is essentially that of a cellular fibroma which in some regions bears a close resemblance to a well-differentiated fibrosarcoma of low-grade malignancy The histologic structure is not uniform throughout any one tumor or in any group of these neoplasms, as it may vary from a dense collagenous tissue with few cells to a cellular fibroma and as stated before ultimately to its most anaplastic expression a well-differentiated fibrosarcoma. It has been previously noted that the diagnosis of dermatofibrosarcoma protuberans as a neoplastic entity is more readily made on the basis of the

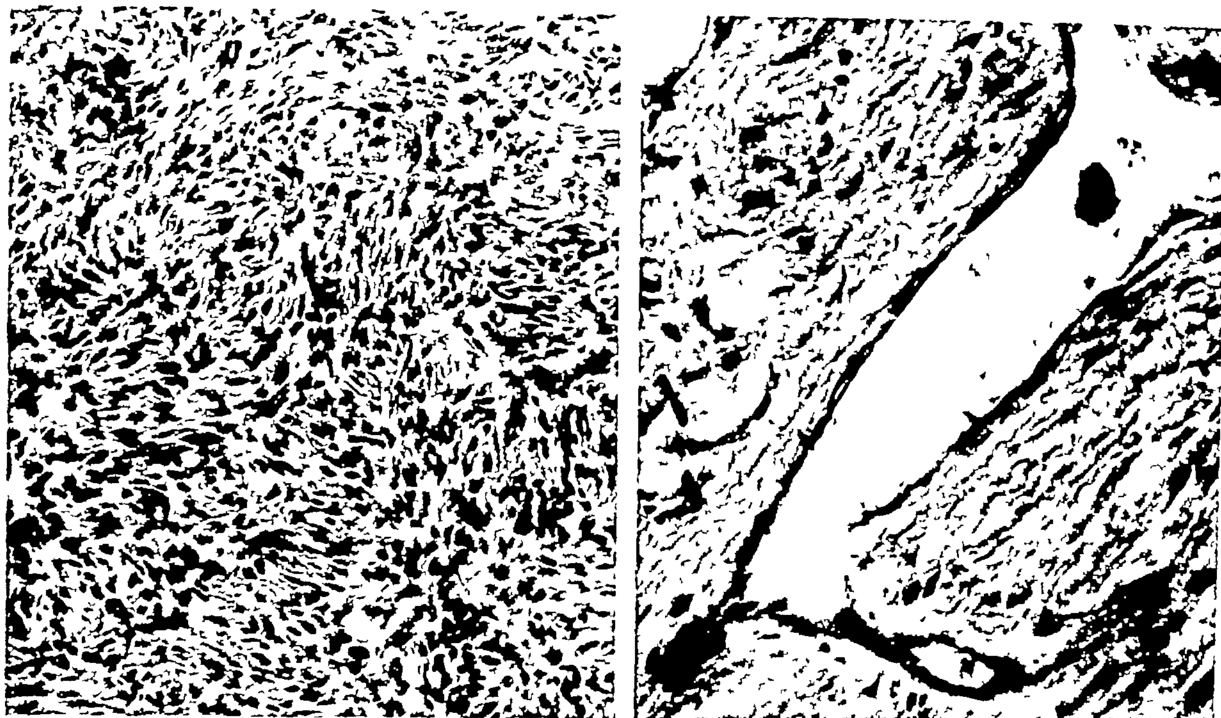


FIG 121 Photomicrographs of dermatofibrosarcoma protuberans (*Left*) Compact interlacing whorls of neoplastic connective tissue (*Right*) The fibrous element of the tumor appears to rest directly or perivascularly on the endothelial lining of the vessels as it does in some sclerosing angiomas (Pack and Tabah, A M A Arch Surg *63* 391, 1951)

clinical history and appearance than it is on microscopic examination, inasmuch as the histologic features are so similar to all the desmoplastic tumors The growth originates in the dermis and, as it develops, encroaches upon the papillae, causing them to become compressed and finally to disappear Because the tumor begins in the corium, it is naturally adherent to the epidermis, which becomes attenuated over the larger nodules and may rupture, leaving an ulcerated surface The epidermal accessories, such as the sweat glands, oil glands, and hair follicles, atrophy and disappear Fine fibrillary projections of the tumor extend subjacent to it and invade the subcutaneous fat lobules The microscope reveals that the circumscription of the lesion is by a pseudocapsule of condensed fibrous tissue

The cellular portions of the neoplasm are made up of fusiform or spindle-shaped cells arranged in whorls or bundles, sometimes around a fine central capillary or lacunar vessel Both Darier and Hoffmann recognized the presence of large lacunar blood vessels within the tumor, a finding so constant that Hoffmann postulated the angiomatous origin of the neoplasm These vascular lacunae are lined by a single layer of endothelial cells resting directly on an investment of fibromatous tumor tissue As would be expected, the more cellular portions of the tumor occur in the actively growing segments, usually the peripheral nodules, per contra, the less cellular and more fibrous portions are in the hard sclerotic and older plaques The frequency of mitoses varies according to the cellularity and rapidity of growth of the various parts of the tumor, but as a rule mitotic figures are rare Large areas of myxomatous and hyaline degeneration are seen Although the microscopic picture may strongly resemble neurofibroma because of the interlacing fibrils, special stains enable one to identify the cells as fibroblasts and the interlacing cells as of connective-tissue origin Mallory's connective-tissue stain may be employed to demonstrate the collagenic stroma Because hemorrhage and deposition of hemosiderin have occurred within the tumor, the inexperienced pathologist has been known to confuse this lesion with melanoma

Is Dermatofibrosarcoma Protuberans Malignant? Does It Metastasize?

The frightening aspect of the well-developed tumor its notorious tendency to recur locally after excision, and the erroneous interpretation of its microscopic features have contributed to an early opinion that it was malignant. The term *dermatofibrosarcoma protuberans* fortunately is a misnomer because the majority of these neoplasms do not metastasize. Its reputation has been maligned because of its known tendency for local recurrence after a presumably wide excision of the tumor, the logical explanation of this complication is unintentional unsuspected, and incomplete initial removal. In these 39 patients there has not been a single instance of metastasis to regional lymph nodes or viscera It may be, however that if these patients are followed for a long time, some instances of metastases may occur to prove exceptions to this opinion inasmuch as, in three later cases, pulmonary metastases have occurred.

From a review of the literature, it would appear that metastases to lymph nodes and viscera are rare but have occurred. This tumor is said to behave more after the fashion of a fibrosarcoma and to metastasize more frequently by the blood stream than through the lymphatics. In Darier s first case a separate nodule developed at a distance of 13 cm. from the original lesion. Although Darier did not excise this second nodule for pathologic study he nevertheless concluded that it represented a secondary metastatic tumor inasmuch as it had the identical clinical appearance of the original lesion. He based his assumption of metastasis on the fact that the skin between the original and secondary tumors felt to be normal We know this conclusion is not valid because microscopic infiltration within the dermis is quite possible over such a distance. His second patient developed a secondary lesion at a distance of 10 cm. from the original one it was excised, but the skin between the two lesions was never removed and examined for evidence of infiltration These tumors may have been of multicentric origin. A P. Stout did not report a single instance of metastasis occurring in his group of 29 cases Bezecny in 1933 reported that 1 of his 3 patients with dermatofibrosarcoma protuberans died of pulmonary metastases, and Sciacchitano in 1935 also related his experience with 1 case of dermal fibrosarcoma which metastasized to the lungs In Binkley s report of 6 cases of dermatofibrosarcoma protuberans published in 1939 he stated that his first patient who had five excisions for local recurrences finally died of metastases 32 years after the original operation. Gate in 1948 described an instance of splenic metastasis from a tumor of this type. Hertzler spoke of these tumors as metastasizing via the lymphatics and reported on lymph node dissections We believe he sometimes confused this tumor with nonpigmented malignant melanoma.

CLINICAL FEATURES

Regional Distribution

As noted by Hoffmann and others this tumor has a greater predilection for the

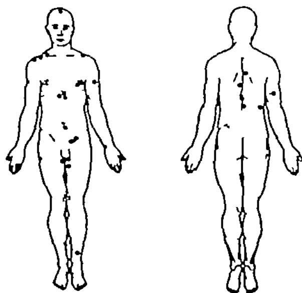


Fig. 122. Regional distribution of dermatofibrosarcoma protuberans. (Pack and Tabah, A.M.A. Arch. Surg. 62 391 1951)

trunk than for the extremities An analysis of our cases showed that the lesion occurred with almost equal frequency on the chest, back, abdomen, upper thigh, and groin (Table 34) Infrequently the neoplasms are situated on the head, scalp, extremities, and genitals

TABLE 34 DERMATOFIBROSARCOMA PROTUBERANS LOCATION OF LESIONS (39 Cases)

Location of Lesion	*Number of Cases*
Sacrum and back	8
Chest	7
Upper thigh and groin	7
Abdomen	5
Supraclavicular region and shoulder	4
Epigastric region	3
Upper arm	2
Wrist	1
Lower leg	1
Scalp	1

AGE AND SEX DISTRIBUTION

The ages of the patients in this report varied from 14 to 87 years, with an average age of 44 3 years, which corresponds to the decennium in which the tumor was most often discovered, namely, 41–50 years (Table 35) Of the 39 patients, 24 (61 5 per cent) were males and 15 (38 5 per cent) were females This sex ratio is almost identical with the figures of Hoffmann, *viz*, 13 males (61 9 per cent) and 8 females (38 1 per cent)

TABLE 35 DERMATOFIBROSARCOMA PROTUBERANS AGE DISTRIBUTION

Ages	*Number of Cases*
11–20 Years	3
21–30 Years	1
31–40 Years	9
41–50 Years	15
51–60 Years	7
61–70 Years	1
71–80 Years	2
Over 80 Years	1

SIZE OF THE TUMOR

The size of the neoplasms when first seen by us varied from 0 5 to 20 0 cm in diameter with the majority in the larger-sized group The largest tumor measured 20 × 15 cm and was composed of many agminated confluent nodules

RATE OF GROWTH AND DURATION OF SYMPTOMS

The rate of growth is imperceptibly slow at first, many years, even, elapsing before the tumor starts to enlarge with increasing rapidity in weeks or months until it may attain a considerable size In our series the known duration of the tumor before medical advice was sought varied from 1 month to 49 years, although in half the cases the patients applied for treatment in 1 to 5 years after the lesions were first noticed The history of long duration of the tumor emphasizes its relative slowness of growth In one of Hoffmann's patients

TABLE 36 DERMATOFIBROSARCOMA PROTUBERANS DURATION OF SYMPTOMS BEFORE FIRST MEDICAL TREATMENT

Duration of Disease	*Number of Cases*
A Lesion present since birth	4
B Lesion present over 30 years and excluding *A*	2
C Lesion present between 21–30 years	1
D Lesion present between 11–20 years	5
E Lesion present between 6–10 years	2
F Lesion present between 1–5 years	19
G Lesion present less than 1 year	6



FIG. 123. Dermatofibrosarcoma protuberans of scalp (Pack and Tabah, A.M.A. Arch Surg 62 391 1951)

the tumor had existed for 50 years in one of Darier's, the duration was 42 years and in two of our group the tumors had been present for more than 30 years In four of our patients, the lesions were present at birth. In them it originated either as a small, raised nodule which manifested growth tendencies in later years of life or else was present as a small bluish-red flat stain in the skin beneath which a small tumor gradually appeared and grew during the ensuing years. These case histories of congenital dermatofibrosarcoma protuberans may be summarized as follows (1) A 35-year-old man had the tumor in the abdominal skin it had grown rapidly for a year (2) A 33-year-old woman had the tumor in the epigastrium, it had grown rapidly for a year (3) A 49 year old woman had the tumor overlying the sternum, it had grown rapidly for 6 months (4) A 42-year-old man had the tumor in the right femoral trigone it had grown rapidly for 2 years

THE CLINICAL HISTORY

The disease has a remarkably uniform clinical history The patient, usually a middle-aged adult presents himself with a growth which is painless but which



FIG. 124 Dermatofibrosarcoma protuberans of trunk (three different patients) (*Top*) Left pectoral region. (*Middle*) Right supramammary region. (*Bottom*) Suprapubic region. (Pack and Tabah, A.M.A. Arch. Surg. 62.391 1951)

has been slowly increasing in size for a number of years Sometimes the first manifestation is reputed to be a flat, red dish-blue or purple mark on the skin at birth or in early childhood. Years later a small nodule appears in the cutis and hypoderm at this identical site and slowly begins its growth More commonly the neoplasm appears spontaneously as a pea sized cutaneous nodule in early adult life. The duration of the tumor before the patient seeks medical attention is generally long

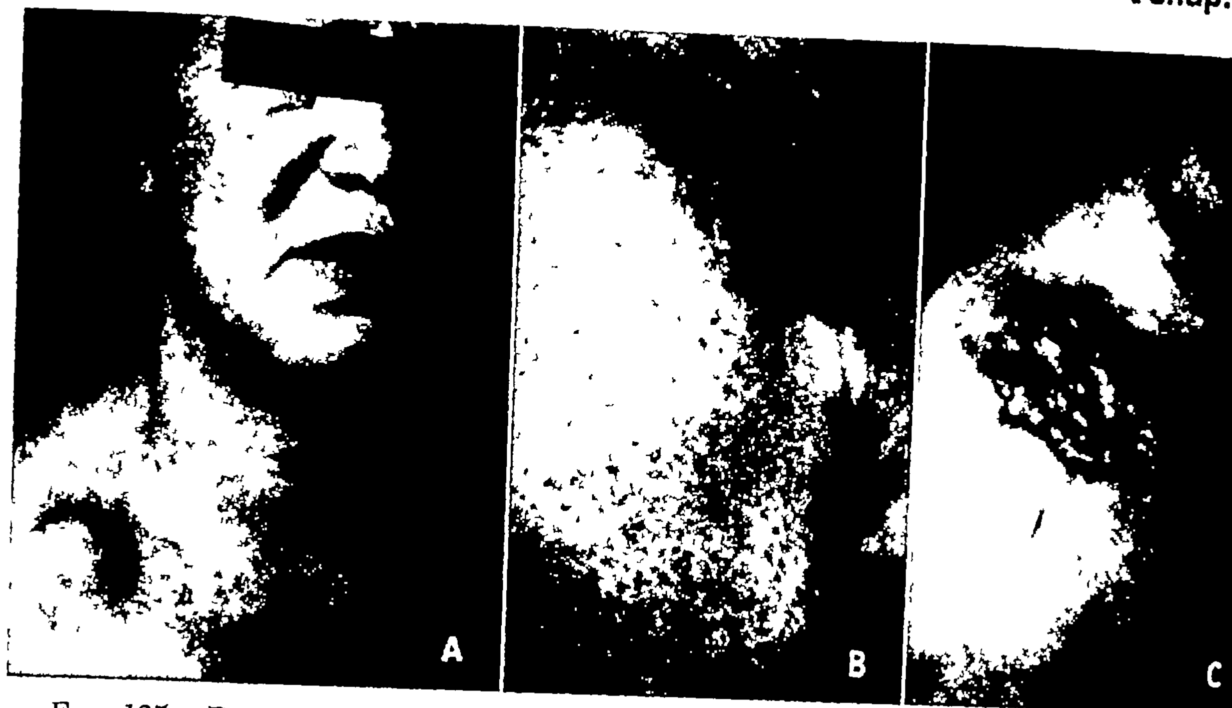


FIG 125 Dermatofibrosarcoma protuberans of shoulder. *A* Right clavicular region. *B* Right pectoral region *C*. Right anterior shoulder region (Pack and Tabah, A M A Arch Surg 62 391, 1951)

Having made its appearance, the small intracutaneous nodularity slowly increases in size by expansile growth, and if more than one nodule develops, they eventually fuse to form a dense fibrotic plaque This elevated plaque remains confined to the dermis and subcutaneous tissues and spreads horizontally as it invades these tissues in an infiltrative manner. The underlying fascia and muscle are seldom involved except as a late complication of recurrent tumors.

After a varying period, usually from one to four years, there appears on the surface of the fibrotic plaque one or more projecting nodular masses. Once they appear, growth of the tumor proceeds more rapidly, and it may enlarge to the size of a man's fist within a few weeks or months. The bosslike projections may occur as hemispheric sessile tumors or more rarely have the appearance of a pedunculated mushroomlike growth In its early stage the entire lesion is quite firm and dense. The overlying skin, which is always fixed to the tumor, assumes a bluish-red or purple discoloration, and as the tumor enlarges the overlying skin becomes thinned and atrophic This may reach such a degree that the least trauma, such as the friction of overlying clothes, may be sufficient to cause the surface to bleed and produce superficial ulceration Once ulcerated, the growth may fungate through as a mass of reddish-brown granulomatous-like tissue, at which stage the tumor is often quite soft



FIG 126 Dermatofibrosarcoma protuberans of anterior trunk Right parasternal region (Pack and Tabah, A M A Arch Surg 62 391, 1951)

The symptom of pain was elicited from 7 of the 39 patients and in none of them was it ever severe or incapacitating The pain was usually of a "shooting" or "burning" character and did not persist for a prolonged time In one patient



FIG. 127 Clinical examples of dermatofibrosarcoma protuberans. (*Left*) Volar aspect of left wrist. (*Middle*) Left femoral trigone. (*Right*) Infraumbilical region (Pack and Tabah, A.M.A. Arch. Surg. 62.391 1951)

the pain was only present during her menstrual period. Pain is certainly not a feature of this neoplastic disease, and, in fact, the lack of severe pain is more characteristic. In some instances the patient may experience discomfort by reason of the location of the lesion, its size, or because of *some injury to it. In only* 4 patients was there a history of bleeding from the tumor· this hemorrhage was of a minor nature only and usually occurred following trauma. Dermatofibrosarcoma protuberans does not affect the general health of the patient, which possibly accounts for the common delay in the institution of treatment.

DIAGNOSIS

An analysis of our cases shows that a correct clinical diagnosis of dermatofibrosarcoma protuberans was made in 16 instances (41 0 per cent) In more recent years the correct clinical diagnosis has been quite consistently made. The next most frequent (and erroneous) diagnoses were neurogenic sarcoma (7 cases) and sclerosing hemangioma (4 cases) Under the microscope and on clinical study the neoplasm has been confused with dermatoleiomyomas originating from the smooth muscles surrounding the hair follicles and apocrine sweat glands. It is histologically similar to the reported picture of dermatofibroma lenticulare or the histiocytoma of Waringer Dermatofibrosarcoma protuberans may so simulate the clinical appearance of the following lesions as to require biopsy diagnosis for identification namely sclerosing hemangioma, desmoid tumor, fibrosarcoma, neurilemmoma, nonpigmented malignant melanoma, sweat gland carcinoma, and wen

TREATMENT OF DERMATOFIBROSARCOMA PROTUBERANS

RADIATION THERAPY

Fibrosarcomas in general are not radiosensitive. Irradiation in itself has not been notably successful in the treatment of dermatofibrosarcoma protuberans McMaster has advocated treatment by wide surgical excision followed routinely by roentgen therapy with the intent to destroy any remaining tumor tissue We contend this principle to be an improper one, implying as it does the use of an inferior method (irradiation) as substitute for an incomplete surgical removal. Irradiation *as the sole means of therapy* has not been used for any of the patients treated initially by our group The combined use of surgical excision and irradiation was employed in seven instances in two of these patients, recur

TABLE 37 DERMATOFIBROSARCOMA PROTUBERANS REPORTED CASES
(Collected from the Literature by Hoffmann)

	Author	Sex Age	Trauma	Location of Lesion	Duration	Treatment	End Results
1	Kartscher	M 71	0	Abdomen	60 yr	Excised 3 times	Died pneumonia after 3rd excision
2	Kartscher	M 55	+	Abdomen	6 yr	Excised 3 times	No evidence of disease, 14 mo
3	Kartscher	F 55	0	Abdomen	7 yr	Excised 3 times	Not stated
4	Pfeiffer	F 61	0	Abdomen	31 yr.	Excised 3 times	Not stated
5	Pfeiffer	M 21	0	Abdomen	15 yr.	Excised twice	No evidence of disease 2 yr after last treatment
6	Pfeiffer	F 53	+	Abdomen	2 yr.	Excised twice	Not stated
7	Coenen	F 61	0	Right shoulder	10 yr	Excised twice	No evidence of disease, 3 yr
8	Coenen	M 53	0	Abdomen	27 yr	Excised twice	No evidence of disease, 8 yr.
9	Arzt	F 45	0	Above left breast	15 yr	Excised twice	Not stated
10	Kuznitsky	F 43	+	Right clavicle	25 yr.	Excised twice	Recurred in 5 yr.
11	Kuznitsky	F 38	+	Right breast	15 yr.	Excised twice	Not stated
12	Kuznitsky	M 22	0	Left chest	15 yr	Excised twice	No evidence of disease, 2 yr.
13	Darier	M 48	0	Abdomen	3 yr	Multiple and varied treatment over 16 yr with recurrence each time	Died pneumonia
14	Darier	M 67	0	Inguinal region	42 yr	Multiple and varied treatment over 35 yr with recurrence each time	Died gangrene leg
15	Darier	F 43	0	Inguinal region	4 yr	Excision	Not stated
16	Darier	M 42	0	Abdomen	9 yr	X-ray	Temporarily regressed but recurred
17	Lutz	M 32	0	Left loin	9 yr.	Excision	Not stated
18	Weidman	M 20	0	Upper thigh	7 yr	X-ray and excision	Not stated
19	Hoffmann	M 57	0	Right buttock	12 yr	Excision	No evidence of disease, 2
20	Hoffmann	M 60	+	Right wrist	50 yr	Excision	No evidence disease, 1
21	Hoffmann	M 49	0	Subscapular region	3 yr	Excision	No evidence disease, 1

rent growths developed 13 months and 4 years, respectively after treatment, the recurrent tumors were successfully removed by surgical procedures Of the remaining five patients, one has been lost for follow up study and the remaining four have been followed for 8 to 19 years with no evidence of recurrence. Although these results are good, we do not believe that radiation therapy adds any worthwhile increment to the salvage of these patients The addition of x ray therapy is not necessary if excision has been complete and if surgical removal be incomplete irradiation may delay but probably not prevent the growth of the residual tumor

Surgical Treatment

The treatment of choice is radical surgical excision, and this opinion is shared with the earlier authors Taylor Pfeiffer Kartscher Coenen Kuznitsky and Grabisch. Darier and Hoffmann commented on the tendency of the tumor to recur following such procedures as cautery excision and the use of chemical caustics Johnston in 1903 advocated an excision so wide that a margin of one inch of normal tissue completely surrounded the lesion The high rate of recurrence of dermatofibrosarcoma protuberans is due to two factors, namely failure to appreciate the infiltrative properties of the neoplasm and consequent incomplete removal. Unless the surgeon succeeds in extirpating beyond the fine projecting rami of the tumor and through completely normal tissue failure follows and recurrence develops If the tumor be small one is generally able adequately to excise it and to close the wound primarily without the use of skin-grafting Although suitable incisions and sliding and transposed skin flaps embodying principles of plastic surgery may close the defect skin-grafting is sometimes necessary We usually have a dermatome immediately available Simple removal of the lesion with circumferential skin and subcutaneous tissue might prove to be sufficient in many cases but due to our own experience with recurrences, we now routinely carry the dissection so deeply that the fascia overlying the muscles is removed with the specimen. The subjacent muscles are excised if the dermatofibrosarcoma infiltrates through the fascia We have never found it necessary to perform an amputation for this tumor If the abdominal wall is the site of origin, careful reparative surgery follows excision in order to prevent the development of a hernia fascia lata grafts are occasionally helpful. The management of metastases in regional lymph nodes has never been a problem as we have never observed this complication Skin-grafting has been done in 6 of the 20 operations for recurrent tumors of this type

END RESULTS OF TREATMENT

If we were to judge the character of this neoplastic disease solely on the basis of our own experience we would consider the title of *dermatofibrosarcoma* generally to be a misnomer because none of these patients has died of the disease or developed metastases Three later patients not included in the tables developed pulmonary metastases Final results are analyzed according to (1) those patients who received their primary or original treatment at the Memorial Hospital (17 cases) and (2) those patients who received their initial treatment elsewhere and came because of recurrent tumors As far as we know all except 2 of the 39 patients are living and well at this writing, although 8 patients (20.5 per cent) developed recurrences after the surgical treatment and were successfully controlled by reoperation

Of the 17 patients who received their primary treatment from us, 14 had wide excisions and 3 had combined operative and radiation therapy Four patients re-

TABLE 38 CASES OF
(Authors'

Case Number	Sex Age	History: Pain	History: History of Trauma	History: Duration to First Treatment	History: Duration to Treatment Here	Physical Findings: Size in Centimeters	Physical Findings: Location	Physical Findings: Color	Physical Findings: Deep Infiltration	Physical Findings: Bleeding	Physical Findings: Ulceration	Provisional Diagnosis at the Memorial Center
1 W B	M 55	Mild, occasional	Yes	3 yr	5 yr	2.5 × 4	Sacral region	Pink	—	No	No	Neurogenic sarcoma
2 L A	M 44	No	No	6 mo	1 yr	0.6 in diameter	Left upper arm	Red	—	No	No	Neurogenic sarcoma
3 H H	F 41	No	No	12 yr	12 yr	4.5 in diameter	Right infraclavicular region	Normal	—	No	No	Neurofibroma
4 L S	M 47	No	Yes	1 yr	1 yr	2.5 in diameter	Right chest	Pink	—	No	No	Infectious granuloma
5 W S	F 74	No	Operative scar 19 yr ago	1 yr	2 yr	13 × 4 × 2 cm high	Left lower abdomen	Purplish red	—	No	No	Neurogenic sarcoma
6 D S	M 54	Shooting pain	No	2½ yr	3 yr	3 × 2 × 1	Left upper chest	Brownish yellow	—	No	No	Cancer developing in sebaceous cyst
7 R E	M 34	Tender 2 mo	Yes, boxer	1 yr	4 yr	17 × 12 × 4	Right upper chest	Dark pink	—	No	No	Liposarcoma
8 A G	M 43	No	No	1 yr	1 yr	3 cm in diameter	Right back	Red	—	Yes	Yes	Dermatofibrosarcoma protuberans
9 P L	F 87	No	No	1½ yr	3 yr	9 × 6	Middle third of right arm	Red	Yes	No	No	Deferred
10 S N	F 30	No	No	10 yr	12 yr	10 × 6	Left sacral region	Dark brown	—	Following slight trauma	No	Neurofibroma
11 R P	M 34	No	No	8 yr	8 yr	2 × 2	Lateral right thigh	Dusky red	—	No	No	Dermatofibrosarcoma protuberans
12 E R	M 59	No	No	2 yr	2 yr	5 × 5	Anterior right shoulder	Purplish red	—	No	No	Cancer developing in sebaceous cyst
13 S W	F 38	No	No	4 yr approximately	30 yr approximately	6 × 6	Volar surface right wrist	Red	—	On trauma	No	Dermatofibrosarcoma protuberans
14 M J	M 54	No	No	1 mo	10 yr	10 × 8	Left upper chest	Pink to red	—	No	No	Dermatofibrosarcoma protuberans
15 G R	M 36	No	No	1 yr	14 yr	10 × 5	Left back	Red	—	No	No	Dermatofibrosarcoma protuberans
16 T W	F 15	No	Pressure from corset, 18 yr	18 yr	18 yr	4 × 3	Right upper abdomen	Bluish pink	Yes	No	No	Sclerosing hemangioma
17 S L	M 46	No	No	2 yr	3½ yr	9 × 7	Left midback	Light pink	—	No	No	Neurogenic sarcoma
18 L R S	F 42	During menses	No	5 mo	1 yr 10 mo	8 × 6	Left groin	Red	—	No	No	Neurogenic sarcoma
19 G T	M 35	Burning, 3 wks	No	Since birth	35 yr	12 × 7 × 5	Right upper abdomen	Purplish red	Yes	No	No	Deferred
20 A M	M 80	No	No	1 mo	1 mo	6 × 3 × 3	Left groin	Normal	—	No	No	Metastatic melanoma
21 S P	F 33	No	No	Many yr (33?)	33 yr	5 × 4	Epigastric region	Brownish	—	No	No	Deferred
22 F S	F 43	No	No	1 yr ap- approximately	3 yr	4 × 3 × 2	Upper, inner left thigh	Red	—	No	No	Papilloma (?)

Dermatofibrosarcoma Protuberans

Series)

Previous Treatment					*Treatment at the Memorial Center*					*End Result*
None	*Excision Only*	*Irradiation Only*	*Excision, Irradiation*	*Recurrence after First Treatment*	*None*	*Excision Only*	*Excision, Irradiation*	*Recurrence after Treatment Here and Further Treatment*	*Skin Grafting*	
				2 yr				None	No	No evidence of disease 19 yr 7 mo.
				4 mo.				None	No	Died 8 yr, 5 mo., malignant melanoma
								None	N	No evidence of disease 10 yr
								4 yr Wide excision	No	No evidence of disease 4 yr 9 mo.
								None	No	No evidence of disease 8 yr 7 mo.
				Lesion persisted				None	N	No evidence of disease 6 yr 5 mo.
				3 mo.				None	Yes	No evidence of disease 5 yr
	Cautery excision			Lesion not destroyed				None	No	No evidence of disease 5 yr 2 mo.
				2 y				None	No	No evidence of disease 1 yr 3 mo. Final
				None						No evidence of disease 8 y 2 mo Patient followed elsewhere
				Incompletely excised				None	No	No evidence of disease 4 yr 6 mo.
								None	N	No evidence of disease 4 yr 10 mo.
				2 wks.				None	Yes	No evidence of disease 4 yr 7 mo.
				1 yr				None	Yes	No evidence of disease 3 y 4 mo.
				9 yr				20 mo. Wide excision	Yes	No evidence of disease 1 yr 8 mo.
								None	No	No evidence of disease 3 yr, 6 mo.
	(1) (2)			7 mo. 9 mo.				None	No	No evidence of disease 1 yr 7 mo.
				5 mo.				None	No	No evidence of disease 1 yr 2 mo.
								None	No	No evidence of disease 1 yr
								None	No	No evidence of disease 6 mo.
								None	No	No evidence of disease 1 mo.
				1 yr				1 mo. Wide excision	No	No evidence of disease 1 mo.

TABLE 38 CASES OF

Case Number	Sex Age	History: Pain	History: History of Trauma	History: Duration to First Treatment	History: Duration to Treatment Here	Physical Findings: Size in Centimeters	Physical Findings: Location	Physical Findings: Color	Physical Findings: Deep Infiltration	Physical Findings: Bleeding	Physical Findings: Ulceration	Provisional Diagnosis at the Memorial Center
23 F G	M 46	No	No	2 mo	2 yr 4 mo	5 cm in diameter	Left supraclavicular region	Bluish	—	No	No	Spindle-cell sarcoma
24 O S	M 52	No	No	17 yr	17 yr	5 × 4	Right lower chest	Normal to light pink	—	No	No	Deferred
25 A C	M 35	No	No	1 yr	1 yr	5 × 4	Right scapula		—	No	No	Dermatofibrosarcoma protuberans
26 L L	M 42	No	No	1 yr	26 yr	10 × 4 × 4	Lower back	Light brown	Yes	No	No	Neurofibroma
27 A B	F 49	No	No	Born with red mark, began to grow as small tumor	26 mo	1 5 × 1	Epigastric region	Red	—	No	No	Sclerosing hemangioma
28 J G	F 14	No	No	2½ yr	3 yr	0 5 cm in diameter	Anterior left lower leg	Normal	—	No	No	Dermatofibrosarcoma protuberans
29 B K	M 57	Yes, 2 wks	No	15 yr	15 yr	6 × 5	Mid-upper back	Pale pink	—	No	Yes	Dermatofibrosarcoma protuberans
30 J P	F 63	No	No	1 yr	23 yr	4 5 cm in diameter	Epigastric region	Normal	Yes	No	No	Desmoid tumor
31 R F	M 59	No	No	33 yr	33 yr	11 × 10 × 8	Right shoulder	Purplish red	—	No	Yes	Neurogenic sarcoma
32 A F	M 42	No	No	Several months	18 yr	6 × 4	Left chest	Red	—	No	No	Dermatoleiomyosarcoma
33 R D	M 42	No	No	35 yr approximately	35 yr	12 × 8 × 5	Right femoral region	Pale pink	—	Yes	No	Neurogenic sarcoma
34 M H	F 27	After standing long	No	Since early childhood	25 yr ?	4 × 3	Right upper thigh	Pink	—	No	No	Sclerosing hemangioma
35 D S	M 20	No	No	5 yr	7 yr	5 × 3	Left lower abdomen	Red	—	No	No	Dermatofibrosarcoma protuberans
36 L S	M 34	No	No	1 yr	2 yr	20 × 15	Upper inner left thigh	Red	—	No	No	Leiomyosarcoma
37 J S	F 18	No	No	2 yr	2 yr	10 × 6	Right supraclavicular region	Bluish red	—	No	No	Sclerosing hemangioma
38 S J	F 41	No	No	32 yr	32 yr	8 × 6	Lower mid-abdomen	Dark pink	—	No	No	Dermatofibrosarcoma protuberans
39 I K	M 41	No	No	1 yr	23 yr	21 × 15	Scalp	Normal	Yes	No	No	Cancer developing in multiple sebaceous cysts

DERMATOFIBROSARCOMA PROTUBERANS (*Continued*)

Previous Treatment					*Treatment at the Memorial Center*					*End Results*
None	*Excision Only*	*Irradiation Only*	*Excision, Irradiation*	*Recurrence after First Treatment*	*None*	*Excision Only*	*Excision, Irradiation*	*Recurrence after Treatment Here and Further Treatment*	*Skin Grafting*	
	(1) (2)		(3)	(1) 6 mo. (2) 1 yr (3) 3 mo.				2 yr 6 mo. Wide 2 yr. excision	Yes	No evidence of disease 1 yr 2 mo.
								None	No	No evidence of disease 3 yr
								None	Yes	No evidence of disease 4 yr 3 mo.
				14 y				None	Yes	No evidence of disease 4 yr 9 mo.
								None	No	No evidence of disease 3 yr 3 mo.
				5 mo.				None	No	No evidence of disease 6 mo.
								None	Yes	No evidence of disease 2 yr 5 mo.
	(1) (2) (3)			12 yr 4 yr 7 yr				None	No	No evidence of disease 2 yr 3 mo.
								None	Yes	No evidence of disease 11 yr 9 mo.
	(1) (2)			7 y 10 y				None	No	No evidence of disease 3 yr
								None	No	No evidence of disease 2 yr 9 mo.
								1 yr Wide excision	Yes	No evidence of disease 5 yr 6 mo.
				2 wks.				1 yr 1 mo. Wide excision	No	No evidence of disease 2 yr 2 mo.
				3 wks.				None	No	No evidence of disease 5 yr 6 mo.
								2 mo. Excision	No	No evidence of disease 2 mo.
								1 yr 4 mo. Excision 10 mo. Excision 9 mo. Excision 8 mo. Excision None	No	No evidence of disease 7 mo.
	Twice			After each operation, last one 2½ yr ago, 1 yr later came here		Partial removal of involved scalp				Operative death, presumably due to anesthesia

quired skin grafts to cover the resultant wound defect Four patients suffered recurrence of their lesions, but all experienced successful re-operations One patient has lived 11 years and 9 months since the date of operation

Of the 21 patients who received their initial treatment elsewhere and came with recurrent tumors, 17 had previous local excisions only, 2 had irradiation, and 2 had combined surgical and x-ray therapy The recurrences following local excision developed after intervals of from 2 weeks to 14 years After irradiation one tumor never completely disappeared, and the other one was again evident after a lapse of 2 years After the combined operative and radiation treatment, the dermatofibrosarcomas regrew in 4 months and 9 years, respectively The disposition of these 21 patients may be adumbrated as follows one went elsewhere for the operation but has been checked repeatedly by us and is well 5½ years later, 4 patients received either preoperative or postoperative irradiation, 16 patients underwent secondary operations Our 4 patients in this series who developed recurrences had tertiary excisions and subsequent freedom from evidence of the neoplasm for periods of 6 months to 2 years The longest period of postoperative follow-up observation without recurrence has been 19 years and 7 months.

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MALIGNANT TUMORS

FIBROSARCOMA

INTRODUCTION

Our knowledge of the natural history of tumors of fibrous tissue has been improved by the brilliant studies of Arthur Purdy Stout, who painstakingly analyzed the histologic features of the numerous tumors catalogued under the heading of sarcoma and presented criteria for a more accurate classification of these neoplasms The *in vitro* technic developed by Murray Stout, and Pogogeff—of growing tumors of the supportive structure from human hosts in culture *media and noting the distinguishing* differential characteristics of these tumors -has contributed an important method of ascertaining the histogenesis *of the various tumors of the soft somatic* tissues.

This chapter reviews the available literature on fibrosarcoma and presents our personal experience with 39 fibrosarcomas of the extremities

DEFINITION AND NOMENCLATURE

Fibrosarcoma in this presentation refers to those malignant neoplasms which arise from fibroblasts The identification and study of true fibrosarcomas has been difficult, because the literature contains numerous examples in which the type of tissue from which the tumor arose could not be determined many of these neoplasms were indiscriminately classified as fibrosarcomas. Paget (1865) designated malignant tumors of fibrous tissue as *recurrent fibroids* Cornil and Ranvier (1880) reported them as *fasciculated sar*

comas, and Bennett (1849) as *fibronucleated tumors* Virchow (1864) described fascial sarcomas as arising from the fascia, usually in the lower extremities, growing slowly, and resulting in cures following surgical removal Birkett (1858) and Billroth (1877) recorded some of the earlier case presentations

Although fibrosarcomas have been the subject for extensive investigation during the past century, very few definite facts have been established about this neoplasm There is a dearth of information to guide the surgeon in establishing criteria for therapy and prognosis This is due to the fact that heretofore many lesions erroneously recorded as fibrosarcomas were either benign tumors (fibromas, etc), with the outcome exceptionally good, or, contrariwise, malignant neoplasms of other types (synovial sarcoma, rhabdomyosarcoma, etc), with the prognosis particularly poor These histologic errors occurred because the prototype cells of the fibroblast (mesenchyme) has multipotential capacities for development and certain neoplasms may present two or more routes of differentiation An example of this is the observation that certain synovial sarcomas will present dense fibroblastic elements throughout the section with an exceptional cuboidal-cell cleft to indicate the diagnostic characteristic of synovial origin

Fibrosarcomas may be mistaken for myxosarcomas as the result of stasis of circulation with resultant edema Foci of calcification or ossification will lull the unwary into a diagnosis of osteogenic sarcoma The perithelial arrangement which certain synovial sarcomas assume has been mistakenly diagnosed as fibrosarcoma because of the theoretical concept of a perithelial membrane of fibrous-tissue structure enclosing small arterioles

Much confusion has arisen pertaining to the differential diagnosis between malignant neurilemmoma and fibrosarcoma Ewing was a leading proponent of the opinion that many tumors of fibrous tissue were of nerve origin He states. "It appears that mesoblastic cells once having been assigned to simple supportive functions have little tendency to neoplastic overgrowth Pure fibroblasts may be drawn into a tumor process, but usually under the influence of more specialized cells, with which fibroblasts are associated, such as epithelium, endothelium, nerve structures, muscle-cells and fat-cells." Adhering to this doctrine, several investigators attributed a neurogenic origin to many spindle-cell tumors of the soft somatic tissues Stout, however, believes that the term *neurogenic sarcoma* has little meaning and states that he has studied the essays on neurogenic sarcoma with faithful attention but has failed to discover what cell type or types produce this tumor, what histologic features are clearly evident by which it may be identified, or any exact or concrete information about it He believes that many malignant fibroblastic tumors involve nerves by infiltration and may be mistakenly diagnosed as of nerve origin He suggests that the term *neurogenic sarcoma* be deleted from all classifications of sarcomas At the First National Cancer Congress in Memphis, Tennessee, in 1949, it was the consensus of the Panel on Soft Tissue Tumors that Stout's point of view be accepted and the term *neurogenic sarcoma* be dropped

Accordingly, the sarcomas of the soft somatic tissues observed on the Mixed Tumor Service at the Memorial Cancer Center were carefully reviewed, and many which had been classified previously as neurogenic sarcoma were reclassified according to new criteria (which will be discussed in more detail under Pathology) and termed *fibrosarcoma* In the light of this reclassification, the analysis of these cases is pertinent, and, it is hoped, will present the salient pathologic and clinical features of fibrosarcoma as they are recognized today.

The nosology of fibrosarcoma is indicated in Table 31 which presents the routes of normal differentiation of tissues from the primitive mesenchyme and the disease entities which may develop from fibrous tissue The chart demonstrates the close relationship of the tissues from mesenchymal origin and indicates why it is not surprising to find more than one cell type and several types of matrix (cartilage bone, collagen, etc) in any given sarcoma.

INCIDENCE OF FIBROSARCOMA

During an 18-year period, there have been 717 patients bearing malignant neoplasms of soft somatic tissues studied on the Mixed Tumor Service of Memorial Hospital, New York City Among these were 39 instances of fibrosarcoma. These cases represent all patients regardless of the extent of the disease or whether or not definitive therapy was given. They include only fibrosarcomas of the soft tissues (the extremities and torso) Those of the head and neck, viscera, and other locations are not included in this report. A microscopic diagnosis was established in every instance Accordingly fibrosarcomas comprise 5 4 per cent of malignant neoplasms of the soft tissues in this series Stout studied 144 fibrosarcomas occurring in the head, neck, trunk, and extremities Of these, 66 involved the extremities

However it is difficult to adjudge the true incidence of fibrosarcomas from the reported series in the literature and to differentiate those which were definitely fibrosarcomas from those which were erroneously labeled fibrosarcoma because of the ambiguity of criteria for defining this particular neoplasm The small number of fibrosarcomas in our large series (717) of sarcomas of soft somatic tissues can be explained by the fact that 261 or 36 4 per cent of these sarcomas were of undetermined histogenesis This is an undesirable category serving as a repository for malignant soft tissue tumors which lack sufficient histologic criteria to permit classification in some one histogenetic group It is our belief that in any large series of soft part sarcomas an appreciable number of these sarcomas of undetermined histogenesis must exist, as they do in this series though we have benefited by the studies of such competent tumor pathologists as James Ewing Fred W Stewart, and Frank Foote. In reports from other institutions, these unclassified sarcomas have been added to the fibrosarcomas, perhaps because of their large component of fibrous tissue elements The fibrosarcomas reported here are a select group with indisputable diagnosis similarity of structure, and behavior The sarcomas of undetermined histogenesis, admittedly more malignant than the true fibrosarcomas were treated with a 41 4 per cent definite 5-year-cure rate. (See Chap 24.)

ETIOLOGIC FACTORS

Fibrosarcomas usually develop spontaneously with no apparent relationship to any etiologic agent. In some instances they apparently may develop upon damaged tissues A better understanding of the genesis could possibly contribute to their prevention

The Role of Trauma

That trauma plays a definite but apparently an infrequent role in the development of fibrosarcoma is indicated by the reports of Melzner who studied the incidence of sarcoma in war wounds during World War I and of Meyerding, who analyzed the material of the Mayo Clinic. Fibrosarcomas occur in scarred or granulation tissue—the *granulation tissue sarcoma* of Ewing (See Chap 4, The Role of Trauma in Inducing Sarcomas.) In no instance of our series could trauma be considered the sole etiologic agent in the formation of fibro-

sarcomas, although a number of patients did complain of injury preceding the discovery of the tumor mass

The Role of Irradiation in the Formation of Fibrosarcomas

There are a number of recorded instances of fibrosarcomas that developed in tissues which were heavily irradiated. Epidermoid carcinomas developing in irradiated skin commonly exhibit spindle-cell metaplasia to such a degree that the tumors have been confused with sarcomas

Congenital Relationship

A congenital relationship is suggested in one of our patients in whom the sarcoma was noted at the age of 6 weeks This was the only such instance

Malignant Degeneration of Benign Tumors

Although several authors have traced the transition of fibrosarcoma from simple fibromas, it is impossible clinically to distinguish fibromas from insidiously growing fibrosarcomas (see p. 44)

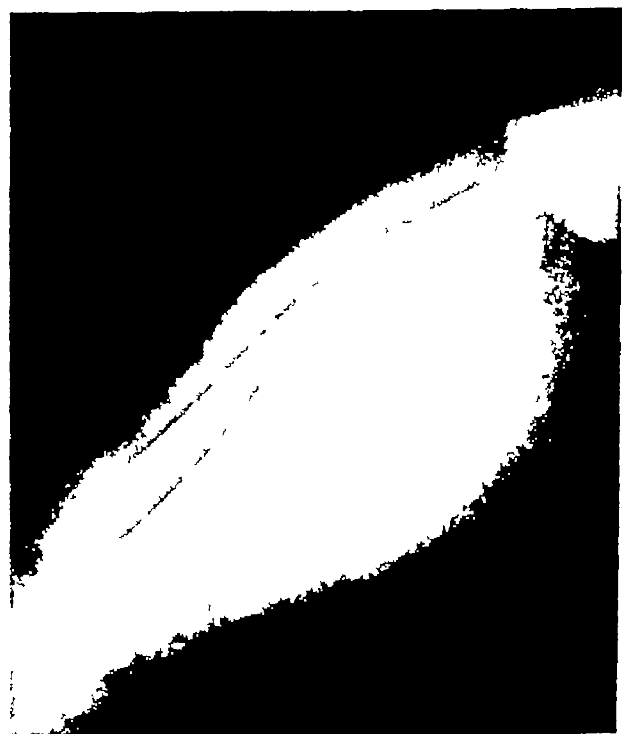


Fig. 128. Roentgenogram demonstrating invasion of ulnar bone by fibrosarcoma (Pack

SEX AND AGE DISTRIBUTION

Sex

There is a preponderance of females in this series Twenty-four of the patients were females and 15 males Others have

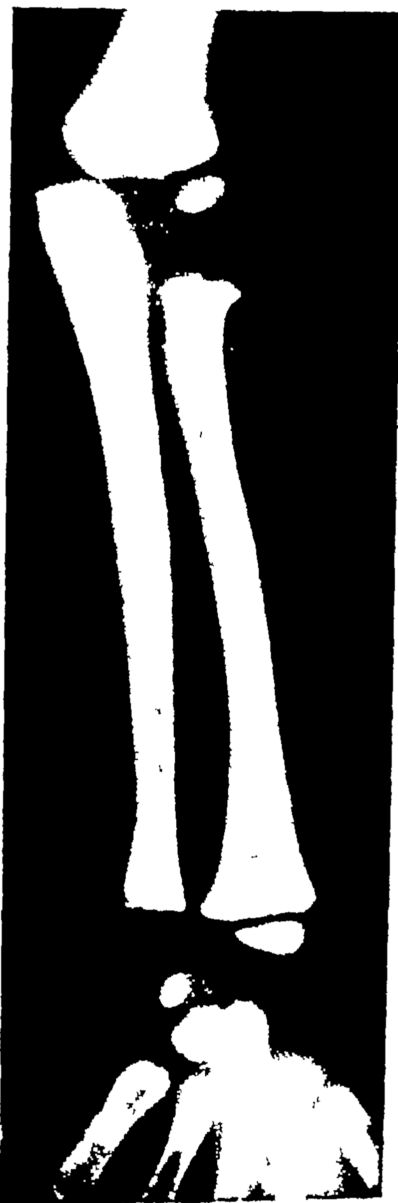


Fig 129 Posteroanterior roentgenogram of same patient as Fig 128, demonstrating repair of osseous defect 3 years after x-ray therapy Patient is alive and free of tumor over 5 years after x-ray therapy, with slight shortening of right forearm but complete function (Pack and Ariel, Surgery 31 [illegible] 1952.)

described a predilection for the male sex, although Heller and Sieber found a slightly higher incidence in females

AGE

Fibrosarcoma is essentially a disease of younger adults The average age of this group was 39 4 years. Fifty-three per cent of all fibrosarcomas in this series occurred in patients between the ages of 30 and 50 years with the incidence gradually and equally tapering off on either side into the younger and older age brackets The youngest patient was 6 weeks old when the tumor was noted, and the oldest was 70 years of age (Table 39) There was no significant dif ference between the ages of the males which averaged 38.3 years, and the ages of the females which averaged 40 years The average age of this group is similar to that of patients bearing synovial sar coma (average age 36.3 years) and those having dermatofibrosarcoma (average age 44.3 years)

Reports in literature indicate a somewhat higher age, but this is probably due to the fact that other types of sar comas may have been included with the fibrosarcomas. Stout and Wilson report a similar age distribution of patients with fibrosarcomas.

TABLE 39 AGE* OF PATIENTS WITH FIBROSARCOMA

Years	0–10	11–20	21–30	31–40	41–50	51–60	61–70	7C
Number of cases	4	2	2	12	8	6	5	0
Percentage of cases	12 5	5 1	5 1	30 8	20 5	15 4	12 8	0

* Age on admission to the Memorial Hospital

LOCATION

Fibrosarcomas occur most frequently on the extremities, and the neoplasms of this report are of the extremities with the exception of seven which wer present on the torso (Table 40) Fibro sarcomas may occur anywhere in th body where fibrous tissue is present an have been described within the ..' tary tract, mesentery omentum, re peritoneal region, liver, breast, centr nervous system, kidney, urethra, vagir lung, mediastinum, upper re tract (including the lip tongue, ... larynx, nasopharynx, nasal cavity) and lower eyelid, etc.

In Stout s series of 218 fibrosarcom observed in the Laboratory of Surgic Pathology Columbia University

TABLE 40 LOCATION OF 39 FIBROSARCOMAS

Anatomic Site	Number of Cases	Percentage Tot..
Upper extremity—*Total*	22	56 4
Shoulder	10	25 6
Arm	3	7 7
Elbow region	5	12 8
Wrist	1	2 5
Hand	3	7 7
Lower extremity—*Total*	10	23 6
Thigh	6	15 4
Knee region	2	5 1
Foot	2	5 1
Back	4	10 2
Chest wall	2	5 1
Abdominal wall	1	2 5

tween 1907 and 1946, 58 occurred s cutaneously and 37 within the muscl tendon, or tendon sheath. Thirty six wer

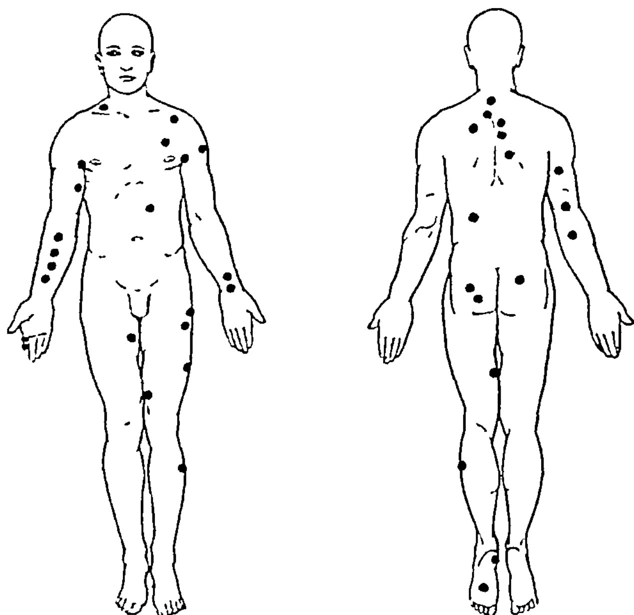


FIG 130 Scattergram illustrating the regional distribution of fibrosarcoma (Pack and Ariel, Surgery *31* 443, 1952)

noted within scars, and 29 were in the skin Next in frequency were those of the abdominal musculature in which he observed 12, and also 12 in the periosteum Meyerding *et al* observed about 184 fibrosarcomas of the extremities The lower extremities were involved most frequently, namely, in two-thirds of the cases It is not surprising that the feet and legs were more frequently involved than the upper extremities because of the greater bulk of fibrous tissue contained within the lower extremities

Yet, in our series the upper extremity was more frequently involved, being the site of fibrosarcoma in 22 instances (56 4 per cent) The lower extremity was invaded in 10 instances (25 6 per cent) and the torso (chest, back, and abdominal wall) in 7 instances The shoulder region was the most frequent location for the origin of fibrosarcoma (15 4 per cent) in the series here reported The thigh was next in frequency, being involved in 6 cases (15 4 per cent) The hands and feet were rarely involved by fibrosarcoma Fibrosarcomas are seldom located about joints The abdominal wall is a common site of fibrous-tissue tumors (desmoid tumors) This interesting neoplastic entity, which occurs most frequently in females and is often related to pregnancy, has been discussed elsewhere in this volume and will not be included here Fibrosarcoma, exclusive of desmoma, has been observed only once to arise in the abdominal wall at Memorial Cancer Center Stout has observed fibrosarcomatous involvement of the abdominal wall (excluding desmoid tumor) in 13 instances in his series of 144 fibrosarcomas of the soft parts

GROSS PATHOLOGIC ANATOMY OF FIBROSARCOMAS

Fibrosarcomas usually originate as small, firm, painless nodules which grow slowly for a long time and may attain a large size before being observed by the patient They are commonly found within the muscles, arising from structural septa, or more frequently, occur subcutaneously in association with aponeuroses At the growing periphery of the tumor, small nodularities develop, sometimes beyond the palpable margins of the fibrosarcoma, these nodularities become agminated, fuse, and are ultimately incorporated in the progressive growth of the sarcoma As a rule the tumor appears to be encapsulated, and large tumors which have developed over

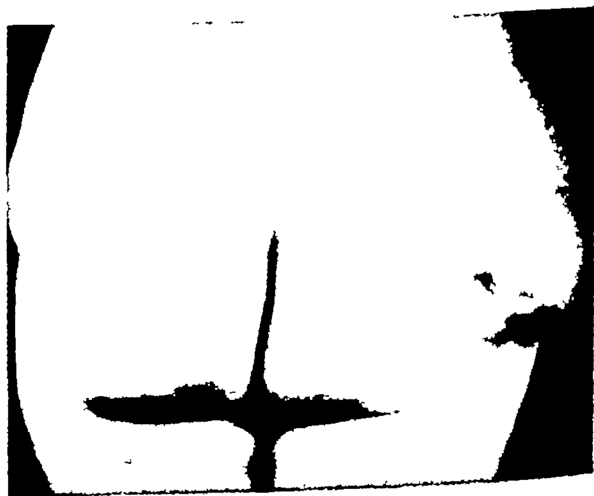


FIG 131 Fibrosarcoma of right buttock which had been locally excised elsewhere 2½ years before The patient developed pulmonary metastases and succumbed 6 months after wide local excision (Pack and Ariel, Surgery *31* 443, 1952)

prolonged periods usually have a thickened capsule, which is intimately attached to the tumor and cannot be separated from it. This is due to small fasciculi extending from the capsule into the tumor sometimes forming lobulations. The capsule can usually be shelled out from its tumor bed. However this is most inadvisable because the tumor may have infiltrated through the capsule and extended into the contiguous structures.

This tendency of fibrosarcoma to force itself against neighboring structures rather than infiltrate them is characteristic and produces some interesting pathologic results. When they occur within muscle groups, they grow to rather bulky proportions because of the yielding nature of the muscular tissue and



Fig. 132. Residual massive fibrosarcoma in the thigh of a 65-year-old female. Status after two unsuccessful attempts at local excision elsewhere before admission. (Pack and Ariel, Surgery 31 443, 1952.)

Fig. 133. Fibrosarcoma involving the right shoulder. Patient is well 5¼ years after interscapulothoracic amputation. Note how the tumor presses against but does not invade the contiguous muscle and bone. (Pack and Ariel, Surgery 31 443, 1952.)

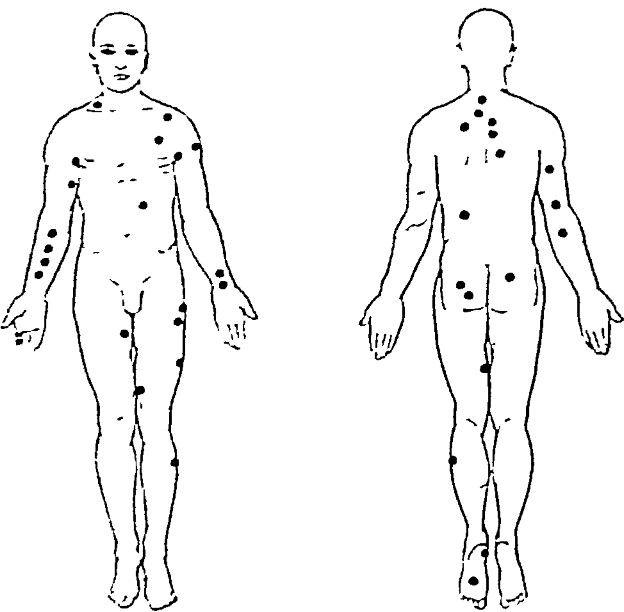


Fig. 130 Scattergram illustrating the regional distribution of fibrosarcoma (Pack and Ariel, Surgery 31 443, 1952)

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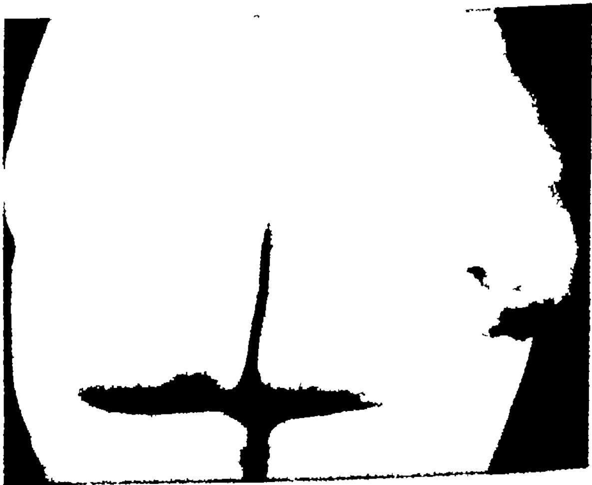


Fig. 131 Fibrosarcoma of right buttock which had been locally excised elsewhere 21 years before The patient developed pulmonary metastases and succumbed 6 months after wide local excision (Pack and Ariel, Surgery 31 443, 1952)

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Fig. 133. Fibrosarcoma involving the right shoulder Patient is well 5¼ years after interscapulothoracic amputation. Note how the tumor presses against but does not invade the contiguous muscle and bone (Pack and Ariel, Surgery *31* 443 1052.)



Fig 134 Clinical photograph and gross specimen of a diffuse fibrosarcoma of the left leg in a 21-year-old female which had invaded bone. Metastases to the lungs occurred 3 months after onset (Pack and Ariel, Surgery *31* 443, 1952)

produce at times a secondary capsule consisting of a thin rim of muscle When they arise from periosteum, that portion which grows into the soft tissue becomes bulky, but that portion which is forced against the bone becomes denser, and the tumor may encircle portions of the bone The response of the pressed bone varies; it usually undergoes pressure atrophy, lending itself to invasion by the neoplasm. Contrariwise, the bone may resist infiltration by cortical thickening and eburnation

Subcutaneous neoplasms may press against the skin, producing pressure atrophy and ulceration either spontaneously or more frequently following trauma. The neoplasm may then fungate This phenomenon does not usually occur, because the tumor tends to follow routes of least resistance and extends along fascial planes Ill-advised attempts at biopsy or local excision may produce the cutaneous break, and the neoplasms may then fungate rapidly through the skin

When they arise close to joints, they may extend into the synovial tissues and be so intimately fused to them that it is difficult to identify the exact point of origin. The tendency of the neoplasm to mold itself against structures with which it comes in contact accounts for the



Fig 135 (*Left*) Clinical photograph of a patient with fibrosarcoma of the hand which infiltrated centripetally to involve a large portion of the left arm, invade bone, produce a pathologic fracture, and infiltrate the chest, compressing the esophagus and requiring gastrostomy (*Right*) Roentgenogram of patient in left figure. Patient living 21 years after known onset of the tumor of the hand. (Case report No 10) (Pack and Ariel, Surgery 31 443, 1952.)

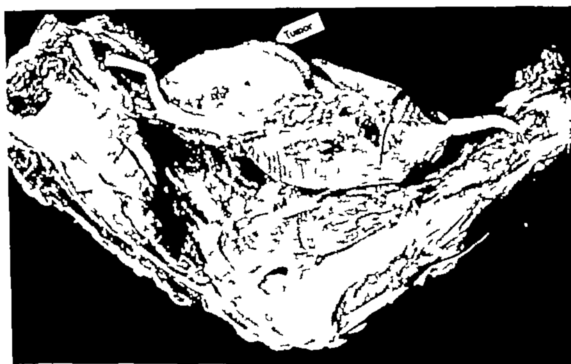


Fig. 136 Fibrosarcoma of the elbow demonstrating how the tumor grows about and involves the nerve. The presence of nerve elements in the tumor may result in an incorrect diagnosis of neoplasm arising from nerve.

rather common finding of larger and smaller nerves and blood vessels traversing the tumor mass.

Because the tumor usually grows in an expansive manner (all portions of the neoplasm contributing to the growth) it is unusual to find large necrotic foci, except in the most malignant fibrosarcomas The tumors are firm to hard in consistence and present a greyish pink



FIG 137 Fibrosarcoma involving right elbow region Unsuccessful attempt at local excision and postoperative x-ray treatment elsewhere 2 months previously. The patient is free of evidence of sarcoma 4 years after wide local dissection (Pack and Ariel, Surgery *31* 443, 1952)

color with a roughened, ropy surface Cut section usually reveals an interlacing maze of fibrouslike strands extending in all directions and presenting a glistening, stringlike surface Scattered sporadically about may be foci of edema, necrosis (rather uncommon), smaller or larger cystlike lesions containing hemorrhagic, dirty red fluid, and regions of frank intratumoral hemorrhage Small deposits of cartilage or bone may occasionally be observed

MICROSCOPIC CHARACTERISTICS OF FIBROSARCOMAS

Fibrosarcomas present features illustrating attempts to continue the normal functioning capacity of the cells, namely, the production of collagen Therefore, variable amounts of stroma are usually present within the neoplasm In well-differentiated fibrosarcomas each cell is contained within a wrapping of slender argyrophilic fibrils These neoplasms in other ways simulate adult fibrous tissue The size and shape of the cells are uniform, the nuclei are spheroid and do not stain deeply. Mitoses are not seen The cells are in orderly arrangement and are dispersed among the abundant collagen stroma which weaves into an interdigitating pattern An occasional blood vessel may be seen, but necrosis is very rarely if ever observed

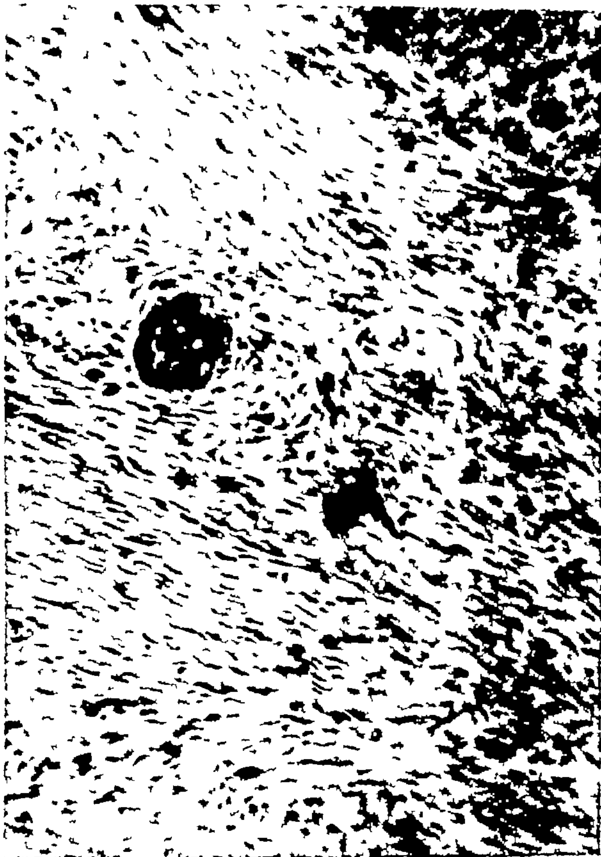


FIG 138 Photomicrograph of a recurrent fibrosarcoma which developed in the right axilla of a 43-year-old female After two recurrences, local excision and interscapulothoracic amputation controlled the neoplasm, and the patient is well 6 years after treatment Note the spindle-shaped cells arranged in a somewhat regular fashion There is an abundance of fibrous-tissue stroma (Pack and Ariel, Surgery *31* 443, 1952)

Along the periphery of the tumor, the structure, although identical to that of the central portions, may have a more flattened appearance, especially if the tumor is pressing against a hard structure such as bone. The cells are more elongated, and the collagen fibers compressed against each other so that the individual autonomy of each strand is lost in the compressed homogeneous structure If the tumor is extending along a fascial plane, this pseudocapsular arrangement is absent, and the cells and collagen of the fibrosarcoma may be intermingled with the cells and stroma of the tissue being invaded (usually muscle) It is to be emphasized that true fibrosarcomas seldom produce structures of other mesodermal derivatives (synovioblasts, osteoblasts, angioblasts



Fig. 139 Photomicrograph of fibrosarcoma of the abdominal wall infiltrating striated muscle. (Pack and Ariel, Surgery 31 443, 1952)



Fig. 141 Photomicrograph of a highly anaplastic fibrosarcoma which developed in the left buttock of a 45-year-old female. The patient succumbed 6 months after onset Note the highly cellular characteristic with loss of polarity and scanty stroma.



Fig. 140. Photomicrograph of a fibrosarcoma which deposits an abundance of collagen stroma. The gross appearance is illustrated in Fig. 133. Note the relative scarcity of cells in proportion to the amount of stroma. The patient is free of sarcoma 5½ years following the surgical extirpation. (Pack and Ariel Surgery 31 443, 1952.)

etc.) and if other structures are noted, especially if one is certain that the foreign structure does not represent the edge of the growing tumor mass the neoplasm is, in all likelihood not a pure fibrosarcoma.

From this well-differentiated rather benign form of fibrosarcoma every degree of increased malignancy may be noted Although fibrosarcomas usually exhibit a rather uniform degree of malignancy throughout the entire tumor a very malignant nidus may be seen in an otherwise well-differentiated tumor

As fibrosarcomas become more anaplastic, less and less stroma becomes evident, with increased crowding of the cells The cells tend to become smaller and hyperchromatic. They do not have a uniform size and shape They tend to lose their spindle shape and become ovoid. Some spindle cells persist. The

nuclei become pyknotic and hyperchromatic. Mitoses may be observed. At the periphery of the tumor, some inflammatory reaction with an occasional giant cell may be seen. Increased tissue edema (probably on the basis of circulatory obstruction), necrosis, and hemorrhage are noted. An increased number of thin-walled capillaries may be observed.

The most anaplastic fibrosarcomas have marked pleomorphism of cells with wide variations in size and shape. Loss of polarity is evident. The nuclei are usually markedly hyperchromatic, and both normal and atypical mitoses are evident. No collagen is present, and a sparse amount of reticulin is seen. No pseudocapsule is present, and there is evidence of patchy necrosis.

METASTASES

Metastases from fibrosarcomas occur infrequently and usually late, although some may metastasize very early. The usual route of dissemination is the blood stream. Meyerding and Pils demonstrated invasion of the blood vessels by soft tissue fibrosarcoma.

The most frequent site for metastases is the lungs, and metastases to this site were observed in nine patients (21 per cent) of this series. Three presented evidence of pulmonary metastases on admission. The average time from treatment at this hospital until pulmonic metastases became evident in the remaining six patients was 6.6 months. It thus becomes apparent that a rather small number of fibrosarcomas will metastasize to the lungs, in contrast to the frequent metastases to this site from the other sarcomas of the soft somatic tissues (synovial sarcoma, 65 per cent, rhabdomyosarcoma, 39 per cent). However, if a given fibrosarcoma is going to metastasize, it does so rather early.

Any organ may be involved by diffuse metastases. Widespread intra-abdominal metastases were observed in several patients of this series after the disease had become generalized.

Although fibrosarcomas usually metastasize by way of the blood stream, on occasion they may metastasize to the regional lymph nodes. This characteristic must be considered in any therapeutic attack. Stout noted metastases to lymph nodes in 8 per cent of his cases, and involvement of the regional lymph nodes was observed in one instance of our series. Examples of metastases by way of the lymphatics are described by Warren and Sommer and by Hertzler. Wilson reported lymph node metastases in four instances.

Metastases have been found in subcutaneous tissues even before pulmonary evidence of metastases was manifest. Wilson quoted two cases in which multiple subcutaneous tumors occurred in widely separated areas, undoubtedly as the result of blood stream dissemination. The feature whereby multiple loci of sarcoma may be observed in one extremity (as in one of our patients) invites speculation as to whether the multiple loci represent metastases from a single fibrosarcoma or whether they are separate, distinct neoplasms. Whichever the explanation, this characteristic of a few fibrosarcomas indicates the necessity for extensive resections in certain instances.

It is of important clinical interest that metastases were noted with relative infrequency (21 per cent) despite the very high local recurrence rate (57 per cent).

SYMPTOMATOLOGY OF FIBROSARCOMA

Fibrosarcomas unfortunately do not present a characteristic symptom complex which could serve to differentiate this malignant neoplasm from benign tumors or other malignant tumors which involve the soft somatic tissues. The most frequent symptom is the presence of a painless mass which starts insidiously, grows slowly, and either [illegible]

huge proportions or, more rarely, causes the patient to seek treatment because of pressure against a nerve which produces pain or other disability The *tumor may* occasionally present itself as a painful mass. Least frequently the onset of pain *with no mass or followed* in a variable time by the presence of a tumor may be the sequence of events. In this series 33 patients (84.6 per cent) presented a painless mass as the initial symptom In 3 patients the initial symptom was a painful mass and in 3 other patients the neoplasm was heralded by the presence of pain with no mass The average delay from onset of the first symptom until establishment of the diagnosis was 32.7 months, a long period of culpability in deed, in the treatment of a malignant neoplasm.

PAINLESS MASS

The fact that the tumors usually arise from subcutaneous aponeuroses, or muscle covering, would make understand able why they would begin as painless subcutaneous masses which would not produce pressure symptoms for a consid erable time. The insidious onset and prolonged growth are characteristic of fibrosarcoma. When first observed by the authors the tumors usually averaged between 4 and 7 cm. in diameter They were not well delineated but seemed to blend gradually into the surrounding tis sue. They were not freely moveable, but the overlying skin could be moved with ease over the tumor (a point of distinc tion from the closely related dermatofibrosarcoma protuberans) The benign ity of the clinical course usually results in undue delay before the patient presents himself for treatment. Thus, of the 33 patients in whom the initial complaint *was the presence of a painless mass*, the average delay from onset of the symptom until the institution of adequate treatment was 2.4 years

The growth characteristics of fibrosar coma *follow one of three* patterns (1) they usually grow slowly from their in ception until they reach a relatively large size (2) they appear to remain stationary for many years before rapid growth occurs or (3) they may grow very rapidly and metastasize early

Slow growth is indicated in two of our patients who delayed 120 to 180 months respectively while the tumors enlarged slowly Three others each delayed 36 months while the tumors gradually in creased in size. Contrary to the above-described benign clinical course was that of one patient whose tumor was present but 4 months before treatment and who died 2 months after thera peutic attempts Another patient also had a highly malignant fibrosarcoma, *her tumor was known to be present for* 1 month before admission and she died 1 month later There were no cases in this series in which the tumor existed as an apparently benign harmless neoplasm for a prolonged time and then suddenly began to grow rapidly

CASE REPORT NO 10: FASCIAL FIBRO SARCOMA OF ARM CONTINUOUS GROWTH EXTENSION WITHOUT METASTASIS DURATION OF 21 YEARS

L. B a 30-year-old woman the mother of nine children, injured the back of her left hand in March, 1928 following which a small lump about 1 cm in diameter appeared. Six months later similar nodules appeared over the lateral aspect of the left upper arm About a *year later the lump on* the upper arm was 10 cm in diameter and the lump on the back of the hand 6 cm. in diameter From this date until seen by us in *April, 1934*, five different operative procedures (namely local excisions) were per formed. At this time the left arm was markedly edematous atrophic, *and* practically useless, with only slight flexion of the fingers and elbow The tumor had ex tended from the dorsum of the hand up the entire arm to involve the entire circumfer ence of the upper arm, the left infraclavicu

lar region, the left axilla, the left scapular region, and the left supraclavicular space A review of the submitted microscopic slides revealed a fascial fibrosarcoma of low-grade malignancy

Treatment

An interscapulothoracic amputation was refused Palliative high-voltage x-ray therapy was given at different times during the succeeding ten years with good growth restraint and slow, progressive diminution in size of the tumors irradiated

The regression became so complete and paresis so improved that three years later the patient was able completely to flex the arm at the elbow In September, 1938, the atrophy of the shoulder girdle, both anteriorly and posteriorly, was very great, but the tumor process was inactive in this location It had extended, however, into the neck where it infiltrated over the isthmus of the thyroid and posteriorly as far as the spinal column, to which the tumor was adherent, causing marked torticollis At this time some difficulty in swallowing was experienced due to pressure on the cervical and upper thoracic esophagus By November, 1938, fluoroscopic and x-ray studies showed the tumor to be extending by direct invasion intercostally into the chest where it was producing a bulky mass within the upper left pleural cavity There was apparently no invasion of the lung but direct growth of the tumor within the chest and continuity with the neoplasm in the region of the shoulder girdle The left first rib was largely destroyed through pressure There was a paralysis of the left phrenic nerve with marked elevation of the left leaf of the diaphragm

At various times within the next two years individual recurrences developed throughout the entire upper extremity, and these were controlled satisfactorily by x-ray therapy and in some instances by palliative surgery or local excision

In August, 1940, the patient experienced inability to swallow even liquids, and a Janeway gastrostomy was performed for feeding purposes, this was used continuously by the patient for the next nine years Her weight had come down from 172 to 92 lbs., but after the gastrostomy feedings, she maintained her weight In 1941 evidence of partial destruction of the left humerus was observed with evidences of bone regeneration following x-ray therapy Three pathologic fractures occurred in the left humerus between 1941 and 1949 Eventually complete paralysis of the extremity occurred and in May, 1949, a disarticulation of the humerus from the glenoid fossa was performed There was no possibility of removing the tumor in its entirety because of its extension within the chest and its tendency to encircle semicircumferentially the left upper neck At no time was there distant dissemination of this cancer

Pathologic Report

At least 20 specimens have been available for microscopic study, and all of them revealed a fascial fibrosarcoma of low-grade malignancy It was considered to be a nonmetastasizing type but one that would tend to recur locally The lesion was never encapsulated The diagnosis on careful study of the disarticulated arm was confirmed The calcified sections of the bone showed no direct invasion of the bone by the tumor.

The course of the disease is typical This patient is living 21 years after the known onset of the fascial sarcoma on the dorsum of the hand and 15 years after application for treatment The process has been one of diffuse, infiltrative, centripetal extension of the tumor from the hand up to and within the thoracic cavity in continuity

Painful and Tender Mass

Of the three patients who complained of a painful, tender mass, it is of interest that all three presented themselves for treatment relatively early, averaging 3 8 months after the onset of their symptoms One patient observed a swelling of the right elbow with numbness and paralysis of the right thumb as a result of pressure against a nerve Another patient detected a painful mass present in the right scapular region, and another complained of a painful mass in the inner aspect of the left thigh which presented itself 4 months after trauma to this region One patient who complained

of a swelling of the right elbow and numbness of the thumb was given antiluetic therapy by her local medical doctor for this symptom without benefit of a Wassermann test, which resulted in a delay of 3 months before the true diagnosis was established and adequate treatment instituted.

Pain with No Mass

Pain without a mass was the chief complaint of three patients, and these patients also sought early medical attention in an average of four months *after the onset of their symptoms* One patient whose initial symptom was pain without the presence of a mass which had been present for a period of seven months before admission revealed a periosteal fibrosarcoma of the left femur for which a hemipelvectomy was performed. A long delay ensued in the establishment of the diagnosis because her local medical doctor diagnosed arthritis for which he gave intravenous injections However since the patient was not relieved, she went to another local physician who also diagnosed arthritis and gave her more intravenous therapy

Another patient also had pain in the medial aspect of the right side, without the presence of a mass for a period of four months after which a mass presented itself at this site. A local medical doctor in this instance referred the patient to the Memorial Cancer Center but the patient did not present himself for a period of a year and a half When he did come, he refused therapy This patient died one year after our examination or two years and eight months after the onset of symptoms for which no therapy whatsoever was given

ROENTGENOGRAPHIC APPEARANCE OF FIBROSARCOMA

There is no characteristic roentgenographic appearance for fibrosarcomas The usual finding is that of a soft tissue density at the site of a soft tissue mass noted clinically Calcification may be present occasionally but was not observed in this series and is not considered of clinical import. When fibrosarcomas arise from periosteum, they may produce atrophy and invasion of the bone, which exhibits a characteristic picture roentgenographically or by pressure against the bone, they may set up a reaction of the bone with cortical ebonization.

Metastases to the chest are identified as localized homogeneous shadows with sharply defined borders They are not infrequently solitary Any patient with a fibrosarcoma and the presence of a discrete density in the lung should be *subjected to thoracotomy for possible* resection.

DIAGNOSIS OF FIBROSARCOMA

It is difficult to establish a diagnosis of fibrosarcoma by any means except microscopic examination of the suspected tissue. All superficial or deeper masses of the extremities should be immediately *suspected as sarcomas* If an asymptomatic tumor has been present for a rather long time (average 3.5 years) in the soft somatic tissues of a middle-aged individual, the diagnosis of a fibrosarcoma should be entertained. The usual small size insidious onset slow growth and asymptomatic nature lull *suspicion* away from the malignant nature of the lesion.

Although roentgenograms do not reveal a characteristic picture they nevertheless do serve to direct the surgeon to the exact site for a biopsy In those instances of soft tissue masses of the extremities in which roentgenograms show evidence either of bone invasion or a reaction of the cortex to the irritative phenomenon produced by the tumor the malignant nature of the neoplasm becomes apparent There *is no method* of establishing the diagnosis of fibrosarcoma except by biopsy

DIFFERENTIAL DIAGNOSIS

Fibrosarcoma must be differentiated from certain benign tumors, other malignant tumors, and the various nonneoplastic diseases of the soft tissue parts Benign tumors such as chondromas and osteomas are usually harder and attached to bone Lipomas are of softer density and are translucent rather than opaque on roentgenographic examination Synovial sarcomas are more frequent in the hands and feet and usually occur closer to the joints Liposarcomas are most frequent in the regions of the retroperitoneum and shoulder and pelvic girdles Other malignant neoplasms which must be distinguished include rhabdomyosarcomas, angiosarcomas, melanosarcomas, and malignant neurilemmomas

PROGNOSIS OF FIBROSARCOMA

The over-all end results following the treatment of fibrosarcomas are better than for other types of sarcomas Earlier diagnoses and the institution of radical surgical treatment no doubt will improve the survival rate of patients bearing fibrosarcomas The data of this series accordingly are analyzed to note those factors which may have influenced the five-year-cure rate The time that the patients were treated by the authors is used as the base line for computing survival periods

Recurrence Rate

Fibrosarcomas are notorious for the high incidence of recurrences which develop subsequent to initial attempts at extirpating the neoplasms Of the 39 patients observed here, 22 (56 per cent) developed a recurrence (Table 41) The average duration from the onset of treatment until a recurrence became clinically evident was 8 6 months The observation that 9 of these 22 patients developed

TABLE 41 RECURRENCE RATE

Total number of patients	39
Number who developed a recurrence	22
Percentage who developed a recurrence	56%
Duration in months from treatment until recurrence	8 6
End results of patients who developed a recurrence	
(a) Number who died	5
(b) Duration in months from treatment of recurrence until death	10
(c) Number who survived 5 years without disease	5
(d) Percentage who were without evidence of disease 5 years or more after treatment of recurrence	50%

their recurrences less than 2 months after the attempt at local extirpation indicates inadequacy of the primary surgical attempts These values include all attempts at excision of the tumor including office procedures by private doctors The high recurrence rate emphasizes the futility of attempting excision except under most favorable hospital conditions with a competent pathologist in consultation and with the surgeon prepared to perform the most radical surgery when indicated Inadequate excision traumatizes the tumor, always results in recurrence, and possibly enhances the occurrence of metastases

It is not uncommon for a second and at times a third recurrence to develop following incomplete attempts at extirpation The usual prolonged time (average 1 5 years) intervening before the onset of a second or third recurrence indicates the relatively benign nature of some of these neoplasms Stout reports a recurrence rate of 60 per cent of soft tissue fibrosarcomas Taylor and Nathanson record 256 cases of which 159 recurred after one or more excisions elsewhere Carroll and Martin record 15 per cent of their 10 cases were recurrent neoplasms when the patient first applied for treatment Wilson described 33 of

207 patients who had had recurrent tumors Beck and Burke also stress the high recurrence rate.

Recurrences develop most likely as a result of pseudopodlahke extensions of the fibrosarcoma through its capsule which persist when excision is limited to decapsulation. Recurrences may also develop as the result of autoinoculation or implantation at the time of surgery due to spillage of tumor cells into the wound. Harrell and Valk have reported an accidental autogenous transplantation of an ulcerated fibrosarcoma at the heel during the application of a pedicled skin graft. They believe this due either to direct extension of the tumor through the graft or to accidental contamination of the incision at the donor site with tumor cells Greene has successfully transplanted human fibrosarcoma into the anterior chambers of the eyes of guinea pigs and carried them through numerous generations

INFLUENCE OF AGE ON PROGNOSIS

It is apparent that the survival rate is higher in the two age extremes Thus the two patients under 20 years of age and the one over 50 years each survived the 5-year period of definitive cure The group between the second and third decades apparently had the poorest prognosis for two patients between 21 and 30 both succumbed of this disease, and three of the seven between 31 and 40 died. Fibrosarcoma is thus different from synovial sarcoma from which no patient over 50 recovered, and the survival rate was much higher in the younger age group

TABLE 42. INFLUENCE OF AGE UPON THE FIVE YEAR SURVIVAL RATE

Age in Years	*Number of Patients*	*Number of 5-yr Cures*	*Percentage of 5-yr Cures*
Under 20	2	2	100
21–30	2	0	0
31–40	7	4	57
41–50	4	3	75
51–60	1	1	100
61–70	2	0	0

INFLUENCE OF SEX ON PROGNOSIS

Females apparently enjoyed a higher incidence of five-year cures Thus 6 of the 10 patients who were apparently free of disease five years after therapy were females The difference is so small that it has no statistical significance.

INFLUENCE OF LOCATION OF TUMOR ON PROGNOSIS

The five year cures were most numerous in those patients with fibrosarcomas of the foot, buttock, and torso. Four patients with fibrosarcoma of these locations each survived five years or longer without recurrence. Fibrosarcomas of

TABLE 43 INFLUENCE OF LOCATION OF FIBROSARCOMA UPON THE FIVE YEAR SURVIVAL RATE

Location	*Number of Patients*	*Number of 5-yr Cures*	*Percentage of 5-yr Cures*
Upper extremity—			
Total	9	4	44 4
Hand	2	1	50 0
Arm	2	1	50 0
Shoulder (including scapular region)	5	2	40 0
Lower extremity—			
Total	8	5	62 5
Foot	2	2	100 0
Leg	1	0	0 0
Thigh	4	2	50 0
Buttock	1	1	100 0
Torso (chest wall back, and abdominal wall)	1	1	100 0

the arm and the thigh each offered a 50 per cent five-year survival rate, and 5 patients bearing fibrosarcomas about the shoulder, including the scapular region, had a five-year survival rate of 40 per cent. One patient with fibrosarcoma of the leg succumbed to recurrence. The Mayo Group and others report a somewhat poorer prognosis for fibrosarcomas of the lower extremities than of the upper extremities.

Influence of Symptomatology on Prognosis

The majority of patients in this series had as their initial symptom the presence of a painless mass. For the 33 patients in this group, the average delay before seeking treatment was 29 months, the five-year-cure rate was 68 per cent.

Three patients complained of a painful mass as the initial symptom, and they presented themselves for treatment on an average of 3.7 months after the onset of the symptoms. Of these three patients one died 4 months after admission, one was lost to follow-up after a year of treatment with no evidence of fibrosarcoma at the time, and the third one is well 20 years after treatment.

Of the patients who complained of pain as the initial symptom, two of the three died within one year after admission, and the third one is well six years after treatment. The fact that the pain heralded the onset of fibrosarcoma suggests that the lesion may have been present for a long time in the depths of the tissues, and therefore a long and hazardous time elapsed before the patient was cognizant of the presence of tumor. The outcome under these circumstances would not be expected to be favorable. Pertaining to this feature, the observation is made that whenever the initial symptom was the presence of a painless mass, the culpability for delay lay with the patient who neglected the slowly growing asymptomatic mass for a long time before seeking medical attention. On the other hand, the patients who suffered pain as the initial symptom usually sought medical advice quickly, but the culpability for delay in establishing the correct diagnosis usually lay with the medical profession.

Influence of Type of Treatment on Prognosis

Until recently reliance was placed usually upon simple excision, either alone or in conjunction with some form of radiation therapy, or upon radiation therapy by itself as the treatment of choice for fibrosarcoma. This conservative treatment combined with the fact that an unduly long time had elapsed before therapy was instituted would preclude expectations for good results. However, when the type of therapy is analyzed to rate the ability of the different methods in effecting a cure, interesting data are revealed (Table 44). Of the four patients who were subjected to surgical treatment alone, all survived the five-year period of definitive cure. Of the two patients whose fibrosarcomas were resected, followed by postoperative irradiation, one

Table 44. Effect of the Type of Treatment at the Memorial Hospital upon the Five-Year Survival Rate

Type of Treatment	*Number of Patients Treated*	*Number of 5-yr Cures*	*Percentage of 5-yr Cures*
Surgery			
Excision	3	3	100
Amputation	1	1	100
Surgical resection and postoperative irradiation	2	1	50
Irradiation followed by surgical resection	4	3	75
Irradiation	6	5	83
No definitive treatment	1	0	0

survived the five year period and for the four patients who received irradiation followed by surgical resection of their tumors the five-year-cure rate was 75 per cent. In all fairness to the choice of therapeutic procedures, it should be stated that the fibrosarcomas receiving preoperative irradiation were clinically adjudged to be less favorable than those which were operated on as the primary procedure. There were six patients who received irradiation alone by us and of these, five (83 per cent) survived five years without evidence of neoplasia All six had undergone a local excision of the fibrosarcomas elsewhere before irradiation was given to the site of the previous local excision as a prophylactic measure. Hence no claims can be made for the role which irradiation may have played in effecting the cure.

One patient had fibrosarcoma, Grade III of the left forearm including the ulnar bone, it was diagnosed six weeks after birth the tumor was treated by high-voltage x rays and Coley's toxin, and the patient is free of evidence of sarcoma four years after treatment. The radiation therapy consisted of x rays generated at 250 kv with 30 ma., 1½ mm. copper filtration, target-skin distance of 50 cm. 250 r per day to the right forearm posteriorly for a total dose of 2000 r in air followed by 250 r daily to the right forearm anteriorly for a total dose of 1500 r in air The calculated tumor dose was 3360 r He was then given a course of Coley's toxin. The mass subsided. Roentgenograms of the involved bone showed marked improvement, and the patient when last seen (four years after treatment) revealed no evidence of fibrosarcoma, muscular atrophy of the extremity was present but no loss of strength was noted

One helpful result of the analysis of these data has been our conclusion that in the past radical surgical measures have been applied too late. Of the 39 patients observed 28 had received some form of treatment elsewhere before coming to the Memorial Cancer Center for therapy Of this group 20 patients had recurrent operable lesions and in 4 (10 per cent) only prophylactic x ray treatment was given. Four additional patients were admitted to this institution after undergoing therapeutic attempts elsewhere, but the fibrosarcomas were too widely metastatic to warrant definitive therapy In only 11 cases (28 per cent) did the patient come with a primary operable neoplasm The observation that 20 patients presented themselves after having had one or more recurrences following improper surgical extirpation indicates that this neoplasm is rather kind to both the patient and surgeon and as a rule lends itself to resection even though traumatized by previous inadequate attempts at surgical extirpation

Irradiation has little to offer in effecting a cure for fibrosarcomas, for they are usually radio-resistant.

Influence of Previous Treatment on Prognosis

In only 3 of the 20 patients available for follow up study was the initial treatment given at Memorial Hospital, and all three enjoyed a five-year-cure rate Of the 17 patients who were initially treated elsewhere, 11 (64 per cent) remained free of fibrosarcoma for 5 years or longer This high survival rate which was obtained despite previous inadequate and often repeated treatment elsewhere resulting in one or more recurrences indicates the relative benignity of fibrosarcomas but emphasizes strongly the inadequacy of surgery practiced by so many in treating this malignant neoplasm

Influence of Degree of Malignancy on Prognosis

The most important prognostic guide is the degree of malignancy manifested

by the microscopic appearance In each instance of this series when the histologic examination revealed a high degree of malignancy (Broders, Grade III or IV), the clinical course was characterized by early and widespread metastases and usually rapid death of the patient The series from the Mayo Clinic clearly corroborates the prognostic significance of the degree of anaplasia of fibrosarcoma.

From this analysis it may be concluded that such factors as age, location, duration of symptoms, etc, play a relatively minor role in affecting the prognosis of patients with fibrosarcoma This is evidenced by the usually long delays before treatment and the high recurrence rate following inadequate treatment, but, notwithstanding, the over-all five-year survival rate is quite high In most cases the histologic appearance of the tumor signified a low-grade malignancy Contrariwise, those patients who reported for treatment early because of rapid growth of the tumor, and who usually died despite early radical treatment, revealed a highly anaplastic neoplasm on microscopic study Fortunately, this type was infrequently encountered (four times)

TREATMENT

The treatment of fibrosarcoma revolves about one of three major disciplines (1) the treatment of the primary lesion when no metastases exist, (2) the treatment of the primary lesion when regional metastases are present, and (3) the treatment of metastases which appear after the primary lesion has been apparently controlled

Treatment of Fibrosarcoma without Metastases

Various therapeutic measures have been utilized: (1) local surgical excision, (2) amputation of the involved extremity, (3) external roentgen irradiation, (4) teleradium therapy, (5) interstitial radon irradiation, and (6) some co[mbination] of these methods Although o[ccasional] cure has been obtained apparently w[ith] radiation therapy in this series, it is c[our] studied conviction that this type of tre[at]ment should never be used as the m[o]dality to effect a cure. Adequate surgi[cal] resection is the only method in the tre[at]ment of fibrosarcoma The extent of t[he] resection depends upon the stage of t[he] tumor and its location The high in[ci]dence of local recurrence so frequent[ly] observed (57 per cent) indicates t[he] futility of treating this malignant ne[o]plasm as an office procedure by loc[al] excision The two proper surgical a[p]proaches consist of (1) a radical surgic[al] extirpation which includes a wide ma[r]gin of approximately 4 to 6 cm of t[he] tumor bed surrounding the neoplas[m] and (2) when this is not feasible, a[m]putation of the involved extremity the only alternative

Whenever fibrosarcomas involve t[he] shoulder girdle and the pelvic girdle, i[.e.] above the shoulder or the hip joint, [or] involve muscles which originate abo[ve] these joints, the amputation must, [of] necessity, be extensive and should co[n]sist either of an interscapulothorac[ic] amputation or a hemipelvectomy Eac[h] of these procedures has been performe[d] by us in the treatment of fibrosarcom[a]. (See Sect II, Chaps 11, 12, 13, fo[r] technics of radical amputation.)

The surgeon should be guided b[y] histologic examination of the resecte[d] specimen, and if the biopsy reveals a[n] anaplastic, highly malignant neoplasm, i[t] is believed that nothing less than an amputation of the involved member can effect a cure unless the tumor is so located that an extremely wide surgical extirpation can be effected Thus, if the *tumor is located within certain muscles*, the entire group of muscles from their origin to their insertion must be radically resected

When the neoplasm arises from periosteum and infringes on bone, the safest procedure is an amputation In those

neoplasms which present a highly differentiated histologic appearance, a segmental resection of the involved bone with splinting of the defect with a bone graft may be performed. Any fibrosarcoma which has infringed upon a joint should be treated by amputation.

Wide local excision may be attempted in those instances in which the tumor has wrapped itself about a major blood vessel or nerve trunk. Because some fibrosarcomas grow in an expansile manner in certain instances the neoplasm may be dissected free from nerve or artery If the fibrosarcoma is of low grade malignancy but infiltrative, a major blood vessel may be resected and the defect bridged by an arterial graft.

Fibrosarcomas which develop in irradiated tissue should have all the damaged tissue included in the resected specimens. Emphasis must be directed upon resection of adequate tissue about the fibrosarcoma. Inasmuch as fibrosarcomas metastasize so infrequently to lymph nodes it is not considered necessary to include a lymph node dissection in all cases However since it does occur (5 1 per cent in this series 8 per cent in Stout s series) when the neoplasm is located close to the regional lymph nodes, the latter may be excised in continuity with the primary tumor This procedure should be performed, of course, wherever nodal metastases are clinically evident.

We do not consider irradiation of value in effecting a cure although in one case of this series a cure was obtained by means of roentgen therapy Hence, if the patient refuses surgery, irradiation may be administered in certain instances We do not use it postoperatively but rely upon adequate surgery for the cure.

In those instances in which a local excision had been performed usually by the family doctor and the patient had then been referred to a cancer clinic, after the malignant nature of the tumor had been discovered, it was the practice at the Memorial Hospital in past years to administer a full course of irradiation to the operative site. More recently the policy is to perform a wide surgical resection of the previous operative site, and the number of cases in which residual sarcoma is found certainly justifies the procedure. A review of the literature shows that relatively few patients have been subjected to radical surgical treatment early in the course of their fibrosarcomas. The combination of a small tumor mild symptoms and slow growth makes the surgeon reluctant to perform radical surgery

Treatment of Primary Fibrosarcoma and Regional Lymph Node Metastases

An important method of therapy for a situation in which neoplastic involvement of the regional lymph nodes accompanies the primary fibrosarcoma is radical excision of the primary and lymph node-bearing regions en bloc. The method for attempting a cure in those instances in which involvement of the upper portion of the extremities requires such procedures as hip-joint disarticulation or shoulder (interscapulothoracic) disarticulation is to perform a radical groin or lower neck dissection respectively associated with the amputation Whenever the fibrosarcoma is located on an extremity but proximal to the elbow or knee, with axillary or inguinal metatases present, and when the primary tumor is movable and suitable for radical local excision, the ideal treatment would be an excision and dissection in continuity to encompass the primary site, the regional lymph nodes and the intervening tissues namely skin fat, fascia, and lymphatics

Treatment of Metastases When the Primary Neoplasm Is Controlled

When regional lymph nodes are invaded by fibrosarcoma, the treatment of choice is radical dissection of the lymph-node bearing region, when technically

feasible, after the manner described previously, that is, in continuity with the primary lesion or in conjunction with amputation If the fibrosarcoma has become fixed to the parietes, has invaded the vessels or the contiguous bones, radical amputation must be performed

SOLITARY METASTASIS TO THE LUNG

Good success is being achieved in the partial or complete resection of a lung-bearing fibrosarcomatous metastasis Alexander has reported that the best results obtained in the treatment of metastatic cancer to the lungs were in metastases from fibrosarcomas Thus, any patient who has had successful local treatment for a fibrosarcoma and who develops metastasis in one lung should receive the benefit of thoracotomy and a lobectomy or pneumonectomy as indicated The unilaterality of pulmonary metastasis should be confirmed by tomographic studies If a patient presents a solitary pulmonary metastasis when he first presents himself for treatment of a sarcoma of the soft somatic tissues, the presence of the metastasis should not deter the surgeon from treating the primary tumor as if no metastasis was present We have performed thoracotomies, segmental resections, and lobectomies for pulmonary metastases from other sarcomas with good palliation, we would do it for fibrosarcomas

PALLIATIVE THERAPY

Deep x-ray therapy, in our experience, has offered good palliation Symptoms arising from pulmonary or skeletal metastases have sometimes responded well to a palliative course of irradiation Although fibrosarcomas are highly radioresistant neoplasms and no reliance should be placed on irradiation for cure, no patient should be denied this modality for palliation, which at times may be excellent

Coley has reported good results in certain instances with combined interstitial and external irradiation No beneficial results have been observed from the use of radioactive isotopes, chemotherapy, or hormonal administrations One of our patients received a protracted course of treatment with ACTH without modification of the course of the disease

END RESULTS OF TREATMENT OF FIBROSARCOMA

Of the 39 patients observed in the authors' series, 13 are alive and apparently free of fibrosarcoma The end results are tabulated in Table 45 Of the 39 patients, only 22 were suitable for evaluation of a 5-year survival rate because 17 patients were observed too recently, that is, within the past 5 years Of the 22 patients treated more than 5 years ago, 13 are alive and free of fibrosarcoma 5 years and longer The absolute 5-year survival rate accordingly is 59 per cent Of this group, 4 patients survived from 5 to 10 years, an additional 4 survived for 10 to 15 years, and there were 2 instances in which the patients survived without evidence of recurrent fibrosarcoma for a period of over 15 years

Of the 22 patients who were treated over 5 years ago, 2 were lost to follow-up study One of these patients, who had a local excision performed elsewhere and received postoperative radium-element-pack treatment at Memorial Hospital, was well and free of disease a year after therapy but refused to return or to answer any of the correspondence pertaining to follow-up data. In the second patient an excision of the tumor followed by postoperative x-ray therapy was accomplished, and he remained well a year after treatment but refused to return for follow-up studies Since it is not possible to know the final outcome of these patients, they may be excluded from the number of cases considered for

TABLE 45 FIVE YEAR END RESULTS IN CASES OF FIBROSARCOMA STUDIED AT THE MEMORIAL HOSPITAL AND PACK MEDICAL GROUP NEW YORK, N Y

Total number of patients	39
Number used to compute 5-year survival	22
(Seventeen patients were treated too recently to be considered in the 5-year survival rate)	
Number alive and free of disease* 5 years or more after treatment	13
Absolute 5-year survival rate	59%
Number of patients lost to follow up before 5-year period	2
Patient 1 well 1 year lost to follow-up	
Patient 2 well 1 year lost to follow up	
Relative 5-year survival rate	65%
(Patients lost to follow up subtracted from total number of patients)	
Number of patients on whom a curative procedure was attempted at the Memorial Hospital	18
(Four patients when first observed suffered from marked pulmonary metastases, and either no treatment or palliative radiation therapy was given)	
Number of patients used to compute therapeutic 5-year survival rate	16
(Patients lost to follow-up [2] and those patients on whom no curative therapy was applied [4] are subtracted from all patients in the series)	
Therapeutic 5-year survival rate	81 3%

* Two patients recorded as failures are alive but with persistent sarcoma 6 years and 8 years after treatment.

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In order to adjudge the efficacy of the therapeutic attempts in this series and to establish a therapeutic 5-year survival rate 4 additional patients are excluded from the calculations because when they first presented themselves at this institution, they had detectable pulmonary and generalized metastases These patients accordingly received no definitive therapy and either palliative therapy was administered to the metastases or no treatment whatsoever was given Therefore, of the 22 patients in only 18 were *curative procedures* instituted. Of these 2 were lost to follow up which leaves a total of 16 patients for whom the therapeutic 5-year survival rate of this series is 81 3 per cent.

This high cure rate, despite delays in diagnosis and treatment and despite trauma induced by previous inadequate surgical procedures, indicates that fibrosarcomas lend themselves well for cure. Reports in the literature giving poor end results in the treatment of fibrosarcoma are due undoubtedly to the inclusion of other sarcomas under the heading of fibrosarcoma. Thus Nathanson and Welch report 63 per cent of their patients succumbed. Stout emphasizes the lack of great malignancy in this tumor by stating that of 144 cases of fibrosarcomas of the soft parts of which 107 were followed, in only 20 per cent did death occur as a result of tumor He states moreover that the figures for fibrosarcomas of all parts are comparable. Heller and Sieber report on 60 patients of whom 37 were followed to death, 12 were living, and no follow up information was available on 11 Wilson of Duke University reported on 111 patients with fibrosarcoma, in which group the mortality rate was 62.2 per cent, 29 7 per cent were well, and 8 1 per cent were still living with residual fibrosarcoma Ivins Dockerty and Ghormley report the experiences at the Mayo Clinic with fibrosarcomas of the soft tissues of the extremities they found that the 5-year survival rate for patients with fibrosarcoma, regardless of the pathologic grade of the tumor and of the form of the treatments employed, was 38 per cent They have classified the relative grades of malignancy according to the method of Broders based on the histo-

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pathologic structure of the tumor, and have revealed that in 8 patients with tumors classified as Grade I, the average survival was 38 per cent, in 8 patients with tumors classified as Grade III, the average survival was 31 per cent, and in 2 patients with tumors classified as Grade IV, the average survival of 5 years was 20 per cent They stress the prognostic value gleaned from the classification of the tumor along with the histopathologic estimates of malignancy

SUMMARY

The pathologic and clinical features of 39 cases of fibrosarcoma are analyzed and presented These cases constitute 5 4 per cent of malignant neoplasms of the soft somatic tissues studied on the Mixed Tumor Service of the Memorial Hospital

As a rule, no etiologic factors were established in this series, although in several cases trauma, scars from burns, scars from abdominal incisions, a congenital relationship, and sarcoma developing in myositis ossificans and in irradiated tissues were observed

There was a preponderance of females among our patients

Fibrosarcoma is essentially a disease of younger adults, the average age was 39 4 years Fifty-three per cent occurred in patients between the ages of 30 and 50 years

The tumors most frequently occur in the proximal portion of the extremities. The most frequent sites for this series were the shoulders and thighs

The usual history is one of a long period wherein a tumor grows slowly over many years There was no characteristic symptom complex or radiographic appearance noted in this series The diagnosis must be established by biopsy Metastases from fibrosarcoma occur relatively infrequently The most frequent site is the lung This was observed in 21 per cent of the cases of this series. If the tumor is of a metastasizing variety, metastasis will develop early in the clinical course

Local recurrences were observed in 56 per cent of this series, usually because of inadequate initial surgical excision The absolute five-year survival rate is 59 per cent The relative five-year survival rate is 65 per cent, and the therapeutic five-year survival rate is 81 3 per cent

Radical surgical excision is the one suitable method of ablating fibrosarcoma Radiation therapy may be used to supplement surgical treatment or for palliation

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MIXED FIBROUS-TISSUE TUMORS

CARCINOSARCOMA OF THE UTERUS*

One of the rare curiosities of gynecologic pathology is the so-called carcinosarcoma of the uterus This malignant mixed-cell tumor of the uterus has the peculiar feature, in common with Wilms s embryonal adenosarcoma of the kidney and sarcoma botryoides of the vagina, of possessing both carcinomatous and sarcomatous elements in its epithelial and stromal structure The tumor is almost invariably polypoid and in the majority of cases originates from the midline of the fundus or posterior wall, this latter fact has influenced some observers to consider the likelihood that it is a developmental anomaly associated with mullerian-duct fusion The polypoid neoplasm may be small or gross, but it is characteristically intraluminal.

Only from 2 to 3 per cent of malignant tumors of the uterus are sarcomas most of these neoplasms are leiomyosarcomas associated with or independent of leiomyomas of the uterus Hertig and Sommers reported 1 per cent of carcinosarcomas among all uterine sarcomas, but this figure is probably high. It is impossible to compute the relative incidence of carcinosarcomas of the uterus but admittedly it is one of the extremely rare malignant neoplasms Many of the tumors reported in medical literature as carcinosarcomas will not bear critical review because some anaplastic carcinomas show marked polymorphism of cells which resemble sarcoma, *e g* the spindle-cell metaplasia found in carcinomas of the thyroid and esophagus and in x ray cancers of the skin In one of our patients a large intracavitary carcinosarcoma of the uterus was found associated with independent discrete leiofibromyomas and an endocervical epidermoid carcinoma (Fig 142)

The first report of a uterine carcinosarcoma is reputed to have been by Rabl Rückhard in 1872. Various instances of double tumors (separate carcinomas and sarcomas) have been reported. Dixon and Dockerty listed 20 instances of mixed carcinosarcomas Lisa *et al.* doubted that many of the reported mixed neoplasms were genuine and accepted only 6 from the literature and recorded 2 others Hill and Miller have reported 4 instances of true carcinosarcomas The term *mixed mesodermal tumor* has been used to describe this complex neoplasm. Stout advises the term *mesenchymoma* because of the common designation of *mixed tumors* for those arising from the salivary glands Cartilage may be found within the tumor and Hill and Miller believe that the cartilage represents metaplasia from epithelial cells

No pathognomonic diagnostic features permit a preoperative appraisal of the character of the tumor The inconstant uterine bleeding (menorrhagia and metrorrhagia) follows no consistent pattern and may be less persistent and profuse than obtains in the cases of the common endometrial cancer

The polypoid tumor is soft greyish pink, and sessile. The surface may be ulcerated or intact Foci of hemorrhage may be seen on cut surface of the lesion. The sarcomatous component with its scarf of endometrial cancer is truly dif

* In collaboration with James R. Lisa and Joseph Gioia.

ferent in microscopic character from the sarcomas occurring in fibromyomas, it is an endometrial stromal sarcoma Lisa *et al* have asserted that the mesenchymal portion of the tumor, *i e.*, the connective-tissue portion, may elaborate intercellular material such as collagen, cartilage, and bone, a circumstance which confirms the mesenchymal genesis of the sarcomatous part Moreover, in the reported cases reviewed by Saphir and Vass, none of the metastases exhibited the combined mixed tumor, that is to say, the metastases were either carcinomatous or sarcomatous However, Nicholson, Goodfriend and Lapan, and Hill and Miller report combined metastases

The intriguing mode of origin of this tumor has puzzled many pathologists, who have suggested several theories (Virchow, Ewing, Herkheimer, Robert Meyer, and Jaffe) Meyer's three groups are

1 *Collision tumor,* in which a primary independent carcinoma and sarcoma arise at different sites and fuse by contiguity of growth Ewing thought of these tumors as mutually invasive

2 *Combination tumor,* in which the two malignant blastomatous elements are derived from one stem cell as in the Wilms's adenosarcoma of the kidney

3 *Composition tumor,* in which the parenchyma and stroma of the single tumor have become neoplastic together (true carcinosarcoma)

Ewing admitted that a common irritant or inciter could simultaneously produce neoplasia of both the epithelial and connective-tissue elements It is conceivable that either the carcinoma or sarcoma could precede, follow, or be coincidental with the other

Virchow, who labeled the tumor as *carcinosarcoma,* believed that within the primary carcinomatous or sarcomatous elements the stromal or epithelial fractions, respectively, were subsequently or simultaneously stimulated to malignant growth

Herkheimer, who preferred the term *carcinomasarcomatodes,* held the occurrence to be more frequent in primary carcinomas, in which the carcinoma stimulates an excessive stromal overgrowth to the point wherein the proliferation becomes sarcomatous

Nothing is known concerning the etiology of this neoplasm, but at least 10 verified cases have received x-ray therapy to the uterus, usually for benign conditions many years before the discovery of the carcinosarcoma

Carcinosarcoma of the uterine body occurs after the menopause, the usual age is in the sixth decade It is of interest that those of the cervix occur during active sexual development and that those of the vagina (sarcoma botryoides) usually occur in children.

The prognosis is almost universally fatal No known patient with this type of neoplasm has survived over five years The average survival from the time of onset is about one year

Local recurrence is the rule, and peritoneal implants frequently occur Distant metastases to the lungs are not uncommon, and metastases to regional lymph nodes are rare but do occur

The only treatment is that which can hope to ablate successfully this malignant tumor, and that is the most radical panhysterectomy Irradiation is almost a worthless procedure as these neoplasms are radio-resistant

The following case illustrates the clinicopathologic features of a uterine carcinosarcoma

CASE REPORT NO 11

N D R , a 64-year-old woman, native of the Philippines, observed slight vaginal bleeding occurring continuously since August 15, 1950, and persisting for a three-week period At that time a diagnostic curettage was performed, the biopsy revealed endometrial adenocarcinoma

The patient had otherwise been in very good health except for slight hypertension

ibetes mellitus which did not require She had given birth to five children t gynecologic complications. One er had had a radical mastectomy for of the breast performed ten years with no evidence of recurrence in erval.

ical examination showed a pale r-old woman with a blood pressure of } who had not sustained any loss of . Except for evidences of hypertension rteriosclerosis, the positive findings limited to the internal genitals The was about twice the normal size but eely movable without evidence of fixa nd with no parametrial induration. ervix was slightly scarred but other iormal.

ative Procedure

September 24 1950 a radical pan ectomy was performed. There was no nce of metastasis within the abdomen. liver was normal. There were no en l iliac, obturator or paraortic lymph . The rectum and bladder were free of ion. The surface of the uterus was th The uterus, the broad ligaments ervix, and a liberal cuff of the vagina removed with the specimen.

the third postoperative week a prophy radium vaginal bomb was inserted for se of 1250 mc. hr against the vaginal ces. She convalesced without compli- n.

s Specimen

e specimen was the uterus with both xa The uterus measured 10 5 cm. in test length 6.5 cm in greatest width, 5.0 cm in greatest anteroposterior diam The portio had a mildly injected surface a vaginal cuff The cervical canal was 1.8 long, the rugae were slightly distorted a pedunculated polyp 4 × 2 × 1 mm e from the anterior wall. From the mid lus arose a piriform yellow white mass × 2 cm. The tip was ragged and hemor gic. The surface was intermittently nodu- nd smooth. The cut surface was homo- cous, fish-fleshed, and relatively soft The : was sharply defined from the myo- metrium to which it was attached. Between its left side and the left horn was an hour glass shaped fibroid 2 4 × 1 8 × 1.4 cm half buried in the myometrium, half project ing into the uterine cavity The submucosal half compressed the piriform mass Its mu cosal surface was smooth The rest of the endometrium was thin and pink grey and had numerous pinpoint clear cysts The myometrium measured from 1 0 to 1 3 cm in thickness, was firm, and had prominent vessels. The serosa was smooth. The right ovary was 1.9 × 1 7 × 1 0 cm and had many small clear cysts. The tube measured 6 7 cm. in length. The serosa had several small cysts. The left ovary measured 2.3 × 1 5 × 0 8 cm. and had a nodular surface and a few small clear cysts. The tube was 5 5 cm. long (Fig 142)

Microscopic Features

The piriform mass was endometrial in nature the glands and stroma intermingled in variable proportion in different areas. The glands were lined chiefly by carcinoma cells, tall, opaque, macronucleated, hyperchro- matic, and rich in bizarre mitoses Some were single-layered, some papillated, some solid nests. The papillated glands were con centrated and closely packed at the tip which showed the result of the curettage Toward the base the carcinomatous glands were associated with dilated glands lined by noncancerous epithelium varying from very flat to tall and hyperplastic. The majority of the stromal cells were malignant, and many were giant in size. Macronucleation and hyperchromatism were marked, mitoses were abundant and bizarre. There was local penetration into the myometrium. Toward the base particularly on the side com- pressed by the fibroid, glands were very scanty Likewise at the base, small areas had normal glands and a very fibrous stroma. The endometrium over the fibroid was atrophic and had a few cystically dilated glands and small, surface, non- malignant papillomas The endometrium in the rest of the uterine cavity was thin and had a few cystically dilated glands and focal marked epithelial hyperplasia. The myo- metrium appeared normal The arteries had intense arteriosclerosis, frequently progress- ing to complete fibrous occlusion. These



Fig 142 The large polypoid carcinosarcoma fills the uterine cavity and the tip presents at the internal os A partially hidden leiomyofibroma is visible in the left horn In the same uterus was an epidermoid carcinoma of the endocervix (Fig 145) (Pack, Lisa, and Gioia, Am J Obst & Gynec 63 1162, 1952)

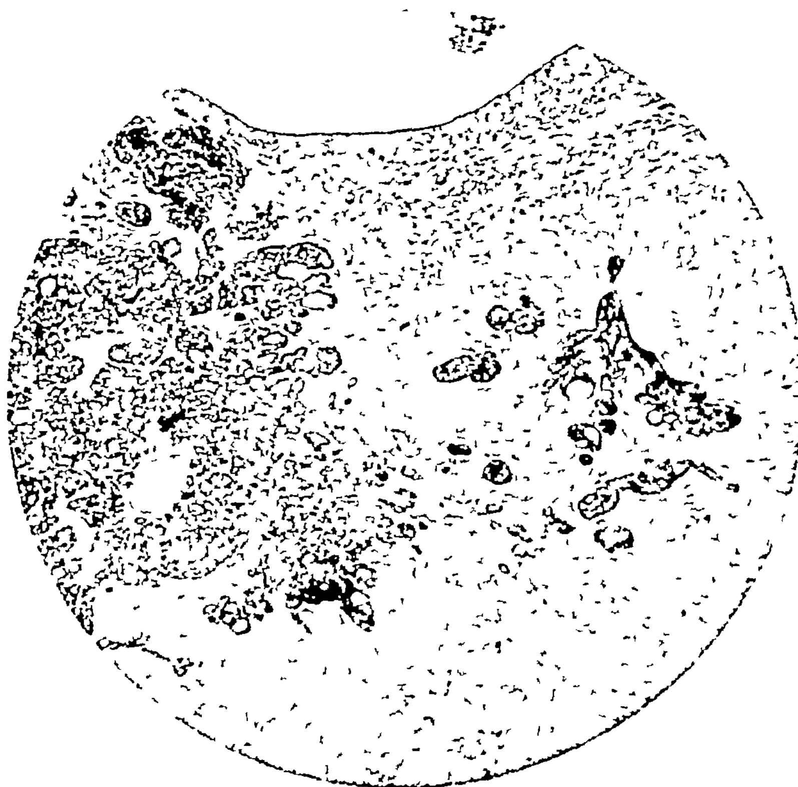


Fig 143 Photomicrograph from the tip of the mass shown in Fig 142 showing both the glandular adenocarcinomatous element and the bizarre cellular stroma (× 15) (Pack, Lisa, and Gioia, Am J Obst & Gynec 63 1162, 1952)



Fig. 144. Higher magnification of Fig 143 showing the glands lined by neoplastic cells having anisocytosis, macronucleation, hyperchromatism and loss of polarity The stromal cells display the same malignant characteristics. (× 400) (Pack, Lisa, and Gioia Am J Obst. & Gynec. 63 1162, 1952.)



Fig. 145 The neoplasm of the uterine cervix. The nests of epidermoid carcinomatous cells are chiefly spindle in shape but some show pearl formation and transitions from one type to the other Associated with an independent carcinosarcoma in the same uterus. (Pack, Lisa, and Gioia, Am J Obst. & Gynec 63 1162, 1952.)

changes were more severe near the masses than in other parts of the uterus

On the portio vaginalis of the cervix to the internal cervical os, the normal epithelium was replaced by malignant squamous epithelial cells mainly of spindle type Near the external os there were a few small pearls and nests of Pagetoid cells At the internal os some of the glands were only partially lined by cancer cells The veins and lymphatics in the lower cervix were widely invaded A rim of normal squamous epithelium covered the edge of the vaginal cuff The arteries were moderately sclerotic The ovaries had several small inclusion cysts containing material varying from amorphous to partially calcified mucus The tubes showed senile fibrosis and small serosal cysts (Figs 143–145)

Pathologic Diagnosis

The diagnosis was (1) primary endometrial carcinosarcoma, (2) postmenopausal endometrium, (3) fibromyoma of uterus, (4) primary squamous-cell carcinoma of cervix, (5) inclusion cysts of ovaries, and (6) serosal cysts of tubes

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CYSTOSARCOMA PHYLLOIDES OF THE BREAST (GIANT INTRACANALICULAR MYXOMA)

DEFINITION AND NOMENCLATURE

In 1838 Johannes Muller collected several specimens of an unusual mammary tumor characterized chiefly by its large bulk, rapid growth following years of dormant quiescence, benign nature, and peculiar gross and microscopic features He considered it a neoplastic entity and called it *cystosarcoma phyllodes* (preferred modern spelling *phylloides*).

This tumor of the breast had been reported in literature several times prior to Muller's classification Chelius had previously given an accurate gross description in which he described this neoplastic entity as one of the most benign diseases to which the organ is subject.

although it presents as a sarcomatous degeneration of the mammary gland and he considered it an impropriety to label it *carcinoma mammae hydatides*

Cystosarcoma phylloides mammae was an uncommon tumor even one hundred years ago It is much less frequent now because the precursory fibroadenomas of the breast are recognized and removed, and therefore the physician today does not see so many neglected cases of advanced mammary tumor

This tumor is not peculiar to the human species, as Bertolet reported the occurrence of a large tumor of one year's duration which was situated in the lower left iliac mammary gland of a nulliparous greyhound with cystic degeneration of the ovaries In this instance the tumor was composed of multiple cysts which were almost completely filled by firm fleshlike proliferations projecting from the cyst walls and which resembled sarcoma in its histologic structure.

The tumor which Johannes Müller termed *cystosarcoma phyllodes* has been designated by at least twenty five synonyms It has been known also as *cystosarcoma papillare cystosarcoma arborescens* and *cystosarcoma polyposum intracanaliculare* Sir Astley Cooper in 1829 included these neoplasms in his group of mammary tumors classified as *cellular hydatids* Sir James Paget called them *glandular proliferous cysts* and Thomas Hodgkin spoke of them as *composite cystoids* Schuh in 1860 included them as a variety of *gelatinous cystosarcoma.* Sir Benjamin Brodie in 1846 gave them the appellation of *sero-cystic sarcoma* Virchow in 1863 used the designation *intracanalicular myxoma* Dietrich, *fibroadenoma intracanaliculare fibromatosum* Leser in 1888 and Noetzel in 1893 *fibrocystadenoma intracanaliculare* Ziegler in 1889 used three different terms namely *cystofibroma papillare sarcome rameux,* and *intracanalicular myxoma* Haeckel in 1894 diagnosed such a tumor as *cystoma papilliferum mammae* Beneke considered this tumor an *adenoma pseudosarcomatodes* Kreibig likewise stressed the point that these cystosarcomas are really *pseudosarcomas* De Quervain in 1908 and Theile in 1909 called the benign tumor of this variety *fibroadenoma phyllodes* and changed the name to *fibrosarcoma phyllodes* in those instances in which the connective-tissue stroma proved to be malignant. Frangenheim in 1930 also designated this tumor as *fibrosarcoma phyllodes* Wohlsecker diagnosed such a tumor as *fibromyxoma intracanaliculare obliterans* because of the tendency of the connective tissue to obliterate the cysts or ducts Binkert used the descriptive term *fibroadenoma intracanalicular sarcomatodes xanthomatodes* Wilms adjudged this tumor to be a congenital variety of adenomyxoma, whereas Coenen considered it one of the *mutation tumors* As Ewing explained its etymology the term *cystosarcoma phylloides* is applied to tumors showing a branching system of more or less parallel cysts recalling the veins of a leaf

Inasmuch as these neoplasms are usually not malignant, the word *sarcoma* cannot be justifiably employed. We have retained the name *cystosarcoma phylloides* because its usage for a hundred years has inseparably associated it with this tumor In modern terminology a suitable descriptive term would be *giant intracanalicular myxoma of the breast*

GENESIS

Mention should be made of the close relationship existing between terminal ducts alveoli, and their enveloping stroma. For instance, the stroma surrounding the terminal ducts and alveoli in the normal breast is relatively cellular and nonfibrous whereas around the larger excretory ducts the stroma is dense and fibrous. It seems therefore, that the connective tissue shares in the functional activity of the terminal ducts and alveoli. Among those studying the development

of intracanalicular fibroadenoma and giant intracanalicular myxoma, a controversy arose concerning which tissue was primarily at fault, the epithelium or the connective-tissue stroma.

Kurn, Leser, Schimmelbusch, and Beneke believed that these tumors derive their primary anlagen from the epithelium of the glands and that the changes in the connective tissue are secondary. On the contrary, Berka, Sasse, and Virchow considered the important factors in their histology to be marked proliferation of the pericanalicular connective tissue with passive increase of epithelium secondary. Haeckel maintained that the ducts dilate first with a consequent invagination by connective tissue. Harpeck ascribed the formation of these intracanalicular tumors to an enlargement of the excretory and milk ducts along their longitudinal ridges. Mornard and Masson mentioned the possibility of origin in galactoceles. Beneke claimed that this tumor owes its development to a blastomatosis of epithelium which may occur at any time in life, the type or degree of stimulation which this epithelium is supposed to communicate to the connective tissue is unknown, but it seems to be delimited somewhat (although irregularly) to the stroma about the walls of the ducts.

In many lactating and resting breasts there is a metaplasia of the periductal and periacinar tissue into myxomatous tissue. When the duct dilates, this myxomatous tissue presumably pushes the epithelium inward by an invagination and becomes papillary by budding. Later the cystic dilatation may be so great as to surround almost the entire projection, forming a cyst (Jungst).

The tendency found in intracanalicular fibroadenomas to form true glands by the extension of ductal epithelium down into the connective tissue is likewise present in cystosarcoma phylloides. These glandular productions in the tumor are probably analogous to the glands in the mammary tissue. The acini in the adjoining breast are frequently cystic.

The ordinary intracanalicular fibroadenoma of the breast is formed as follows. The inner or subepithelial layers of the pericanalicular connective tissue participate more actively in the growth of the tumor than do the outermost connective-tissue layers, in consequence of which buckling or folding of these inner layers occurs, and rounded or papillary projections of the periductal tissue are invaginated into the lumina of the tubules. The same explanation may be valid for cystosarcoma phylloides. Treves and Sunderland have observed the greatest overgrowth of fibrous tissue to occur adjacent to the epithelial structures.

Reinhardt was the first to demonstrate that cystosarcoma could develop from fibroadenoma of the breast. In describing this transition, Billroth said that if the stroma enlarges intracanalicularly, then either obliteration of the lumen occurs or these lumina enlarge to cover the stromal proliferation. Another factor to which enlargement of the ductal lumina was attributed was secretion, which caused the intraductular projections to resemble polypoid tufts. Frangenheim and Ribbert independently asserted that a particular type of intracanalicular fibroma was precursory, because in this variety the periductal and periacinar connective tissue seem quite embryonic. Beneke also attributed the origin of cystosarcoma phylloides to preexisting fetal adenomas, on this account they were said to retain their embryonal capacity to proliferate. Frangenheim explains that cystadenomas are transitional stages between fibroadenomas and cystosarcomas. Schimmelbusch said that cystosarcoma phylloides was merely an advanced developmental phase of fibroadenoma and, therefore, should not be called sarcoma since it was a benign tumor. True malignant tumors may orig-

inate, however in benign mammary fibrosarcoma. In such fibroepithelial tumors the epithelium may become carcinomatous, or both fibrous and epithelial tissue may become malignant (sarcocarcinoma) as described by Coenen and by Wehner Virchow knew that sarcoma could originate in the stroma of an epithelial tumor Ehrlich showed, when transplanting carcinoma of a mouse into different animals, that the stroma may change so as eventually to replace the carcinoma and finally become sarcomatous The mechanism of stimulation in these instances as in cystosarcoma phylloides, may be similar in kind if not in quantity

Krompecher and Sasse believed that cystosarcoma phylloides may originate in the fibroadenomas developing in breasts which are involved in diffuse fibromatosis but the majority of pathologists accept the congenital origin (theory of Cohnheim) These authors notably Wilms, insist that the anlagen of these tumors are embryonal tissue anomalies included in the region of the breast. The delimitation of the tumor by capsulation and the lack of infiltration indicate the separate entity of the tumor and contradict the theory of its origin from adult breast tissue.

ETIOLOGIC INFLUENCE OF LACTATI AND PREGNANCY

Finsterer concluded from his stuc 18 cases that cystosarcoma could b pected to develop in breasts which reached the climax of physiologic f tion by repeated births and lactat Helmuth, on the contrary observed they usually appear in the breasts o married and childless women. It is opinion that repeated births and l tions are the most frequent stimuli t metamorphosis of fibroadenoma into tosarcoma phylloides It is generally known that the ordinary fibrosarc participates in the hypertrophy w the breast undergoes during pregn and lactation Moreover the histori these patients state definitely that tumor acquired a marked growth u tus during pregnancy lactation, menopause. Physiologists have known that whenever there is functi proliferation of epithelium in the se cycle, such as in the breast and ut there is a corresponding activity expressed in mitosis in the stroma cent to the epithelium. In a similar n ner the stroma of the intracanali fibroadenoma participates in the stin tion by pregnancy and lactation.



Fig. 148. (*Left*) Clinical photograph of cystosarcoma phylloides reported by Helmut in 1871 (Lee and Pack, Ann. Surg. 93 250 1931.) (*Right*) Clinical photograph of pa tient with cystosarcoma phylloides. Note the size of the affected breast, the livid intac skin, and the protuberant elastic eminence in the inner segment. (Lee and Pack, Am Cancer 15 2583 1931.)

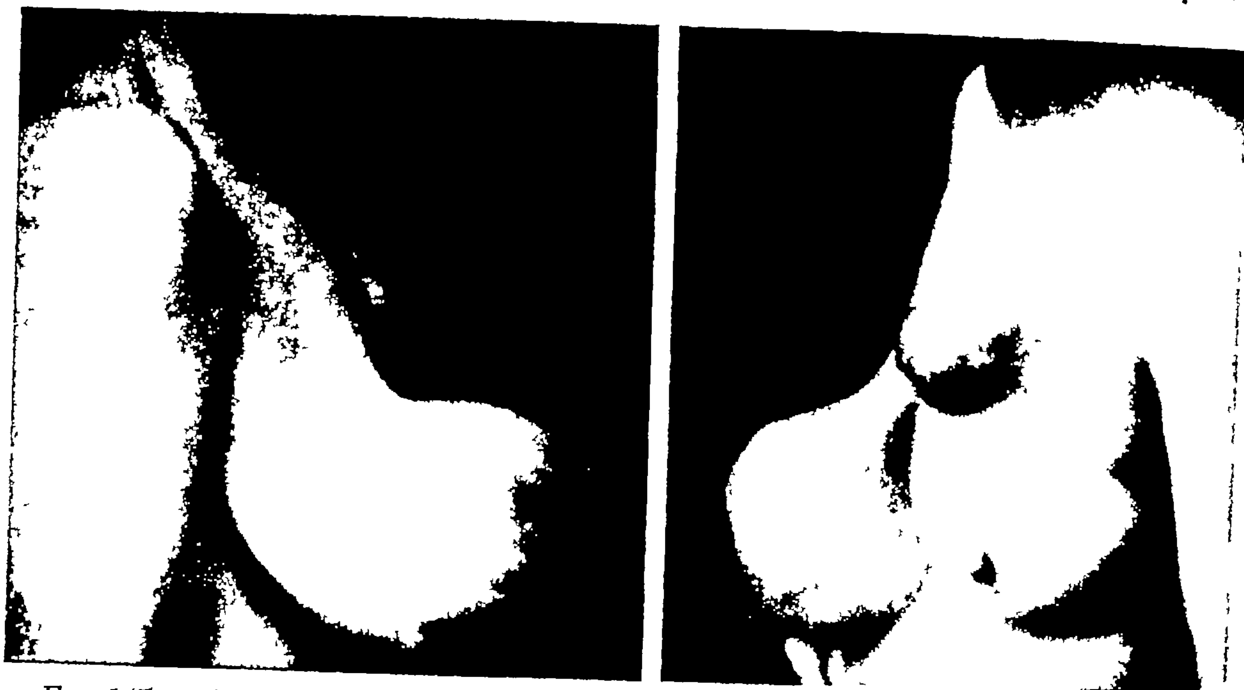


FIG 147. Clinical photographs of patient with giant intracanalicular fibroadenomyxoma of right breast, bulky adenocarcinoma of left breast. (Lee and Pack, Am J Cancer 15.2583, 1931.)

In 91 instances in our collective series of 109 cases, the marital state of patients was given, 15 (16 5 per cent) were single In 38 reports the number of children was stated 9 had 1 child, 8 had 2, 6 had 3, 1 had 4, 2 had 5, 5 had 6, 2 had 7, 2 had 8, and 3 had 10 children On analysis we find that the average mother in this group had 4 children

Several of the cases illustrate the significance of these factors One patient, a para 2, and another a para 6, had never nursed A third patient nursed her children from her normal breast but never from the breast in which the tumor developed because of deficient secretion Another woman, a para 6, nursed her children on the left breast only, the tumor developing later in the right breast One patient, a para 6, observed that with each pregnancy the tumor would increase in size but would remain quiescent during the nonpregnant intervals, she never nursed from the breast containing the tumor because of a retracted nipple, although this breast lactated at the completion of each pregnancy In another instance the tumor became swollen with each menstrual period Two patients volunteered the information that lactation stimulated the growth of the tumor. Another woman was pregnant at the time the tumor was extirpated Still another had only 1 child, nursed this child, and later served as a wet nurse for 2 other children In a 30-year-old woman menstruation ceased spontaneously, whereupon an arrested inactive fibroadenoma grew with great rapidity A 39-year-old woman, a para 5, noticed the appearance of a tumor immediately after her last childbirth, which was followed by a sudden and permanent amenorrhea

PATHOLOGIC ANATOMY

GROSS APPEARANCE

Sir Astley Cooper reported several cases of hydatid disease of the breast, but all were not cystosarcoma phylloides

The early writers encountered much later stages of these neoplasms than are now commonly seen Grossly the tumor tends to fall apart because of the enormous clefts and polypoid masses On hemisection of such a tumor, the intracystic contents are frequently packed so tightly that when the polyps are lifted out of the cyst they cannot be replaced

FIG. 148. Gross specimen of a giant intracanalicular myxoma of the breast. There is marked overgrowth of the stroma in lobular arrangement; some of these lobules appear myxosarcomatous when examined microscopically. (Lee and Pack, Am. J. Cancer 15:2583, 1931.)



FIG. 149. Gross specimen of giant intracanalicular fibroadenomyxoma of the breast. Note the gross lobulations and the tendency of the tumor to fall apart (the cockscomb feature).

These polypoid projections may be described as cone-shaped, nodular, sessile, papillary, cauliflower, warty, arborescent, lamellar, teatlike, fingerlike, or mushroom in appearance These intracystic polypoid masses have been referred to as *papillary elephantiasis* Virchow, Orth, and Ribbert compared this tumor to a cabbage because of its frequent laminations, on section, layer after layer of flattened lamellae can be removed The polyps are visible to the naked eye, sometimes projecting from broad pedicles into the cysts with dendritic fimbriated extremities resembling a cock's comb On pressure the polyps mutually flatten each other, which so distorts them that they become tortuous Some of the polyps are flat and arranged like the leaves of a book The polyps may become adherent to the opposite wall

The masses may fill the clefts so well as to simulate a solid tumor On cut section some regions appear solid like sarcoma and microscopically may be pseudosarcomatous The anastomotic clefts appear as sinuosities, these clefts are the old dislocated cavities of the ducts Such lacunar slits in the tumor substance are supposed to be diagnostic of a benign neoplasm The cystosarcoma phylloides may be multilocular, the cysts are often confluent due to rupture of intervening septa

Only a thin layer of straw-colored fluid may exist between the vegetations and the cyst wall In other instances the secretion is mucous, gelatinous, or oily, or it resembles old extravasated blood, at times the fluid is granular due to its content of keratinized flakes The liquid is a secretion of the epithelium of the cysts, modified by long residence in the cysts, leukocytes are frequently present

The stroma is commonly myxomatous and seems loose and gelatinous It may be smooth, striated, glistening, yellowish-white, grey or reddish-grey, and telangiectatic Occasionally hemorrhages occur from the delicate blood vessels in the tissue stroma The capsule of the tumor may be highly vascular, thin, and transparent The tumor does not usually invade the adjacent breast tissue and thereby lacks the destructive ability of malignant neoplasms. The neighboring breast tissue frequently contains enlarged, dilated ducts, presumably caused by pressure In the same or opposite breast other fibroadenomas may be seen in various transitional stages of gelatinous metamorphosis or forming new cystosarcomas.

PATHOLOGIC HISTOLOGY

The giant intracanalicular myxoma, in common with the intracanalicular fibroadenoma, derives its stroma from the subepithelial connective tissue (mantle tissue) that exists between the epithelial cells and the elastica When such tumors are studied, it is realized that the bulky stroma is not simply an increase of connective tissue but has characteristic qualitative changes as well It is a heteroplastic type of interstitial connective-tissue proliferation The myxomatous character of the stroma is the most constant feature in cystosarcoma phylloides. When the metamorphosis occurs with replacement of the connective tissue by myxomatous tissue, then the tumor increases rapidly in size This is an expansive rather than an infiltrative growth Only certain lobules of the tumor become myxomatous These myxomatous changes are more pronounced within the polyps than in other interstitial tissues of the tumor Under the microscope these regions have the appearance of an interlacing meshwork of star-shaped cells and fibers Marked overgrowth of fibrous tissue is a characteristic of this disease process

The tumor cells are often radially arranged around the blood vessels This perivascular distribution is also seen in sarcoma The spindle cells of the stroma tend to run parallel to the elongated

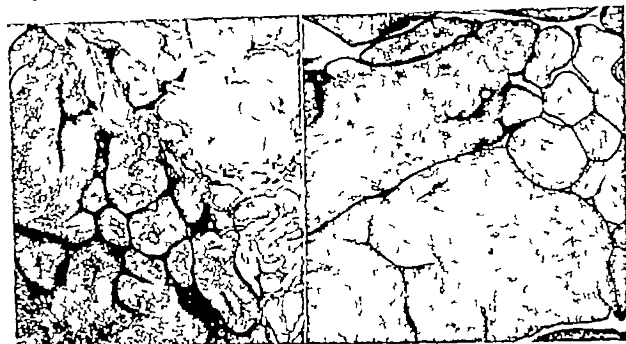


FIG. 150 Photomicrograph of cystosarcoma phylloides of the breast, more properly termed *giant intracanalicular myxoma*, a desmoplasia often influenced by hormonal changes.

clefts The firm portions of the stroma are composed of fusiform cells with bizarre nuclei, which are narrow and rod like, resembling smooth muscle nuclei. The variability of the size of the stroma cells and nuclei resembles sarcomatous tissue However mitoses are rare in cystosarcoma and true atypical cells are lacking. Jungst asserted that this peri glandular metaplastic tissue was degen erative because he found the nuclei of the cells to be bare.

Bulky necrosis is never common, as occurs in true sarcoma. The blood ves sels of the stroma are delicate and em bryonal perivascular infiltration of lym phocytes and plasma cells may be seen many of the blood vessels are throm-bosed. Cholesterol crystals are some times seen between the tumor cells Giant foreign body cells with multipolar kinesis engulf these cholesterol crystals Some of the giant cells contain intra cellular doubly refractive fat which has been attributed to abnormal metabolism. Just as xanthomatous changes are fre-quent in degenerating breasts, so they are often seen accompanying inflamma tory changes in these tumors Hyaline changes occur diffusely thereby decreas ing the vascularity of the tumor Hyaline metamorphosis affects particularly the polypoid tissue, and the individual polyps decrease in size in this hyaline degeneration because of lessened edema. The hyaline may become delimited in the center of the polyps to form definite hyaline beads Russell bodies are prod ucts of hyaline degeneration and are oc casionally seen in these tumor cells Calcareous deposits and pigment accum ulation may occur in the stroma of the tumor

The ducts of the tumor are so dilated and tortuous that no one microscopic section can ever show the entire course of one duct. The ducts become tortuous because of the connective-tissue invagi nations The ducts are the dividing tracts of the connective tissue. These very nar row ducts may grow into pseudosar comatous structure however, they do not form true acini. In no place is there ever any independence of the stroma proliferation from the ducts

Not all of the polyps are covered with epithelium, as some have become de-nuded by pressure or irritation The ma jority of these giant intracanalicular myxomas have clefts lined by cylindrical

or cuboidal epithelium This cuboidal or columnar epithelium of the clefts may undergo metaplasia to form pavement epithelium, even true epithelial pearls, indicating a functional stability

CLINICAL FEATURES

Age

The giant intracanalicular myxomas of the breast usually develop from preexisting intracanalicular fibroadenomas Intracanalicular fibroadenomas occur in the breasts of women who are generally older than those in whom occur the pubertal fibroadenomas which develop from the pericanalicular and periacinar connective tissue The average age of 109 patients with cystosarcoma phylloides was 44 6 years, in single women the average age was 45 3 years The average age of patients with fibroadenomas of the breast was 35 years, single women were 12 years younger than the married woman who had this particular tumor The average known duration of cystosarcoma phylloides in this series was 6 7 years, therefore, when this figure was subtracted from 44 6, the average age of the patients, we obtained 37 8 years, which is the estimated average age when the tumor first appeared This age of onset is not significantly greater than the normal incidence for mammary fibroadenomas Sometimes this tumor originates shortly after the onset of puberty

Symptomatology

The three clinical features which distinguish this tumor from other mammary tumors are the presence of a precursory tumor, rapid growth, and attainment of unusual size In Finsterer's 18 cases pain occurred in 6 instances, it was never present in the early stages but appeared only when rapid growth occurred, with pressure and tension on the overlying skin. In our collective series the initial evidence in 67 women was the discovery by the patient of a palpable lump in the breast Two patients stated that the initial sign was a discharge from the nipple, this is quite infrequent and is not the usual accompaniment of cystosarcoma phylloides Only 4 patients stated that pain in the breast was the initial symptom, but 19 complained of the presence of pain in later stages of the disease Seven women complained chiefly of the great inconvenience caused by the weight of these heavy tumors Only 8 of the 109 patients had a constitutional impairment of health The general health remains good in spite of the tumor Cachexia, loss of weight, and anemia never occur unless ulceration, infection, and hemorrhage alter the local condition

Physical Signs

The usual giant intracanalicular myxoma of the breast is a bulky, freely movable, encapsulated, nonadherent tumor with bosselated nodulations, variable regions of fluctuations, and resistance unaccompanied by retraction of the nipple or palpable axillary lymph nodes The lobulations and inequalities of the tumor are easily felt through the skin The smallest tumors are smooth, even, and regular in shape, occasionally they are disc-shaped Fluctuation is frequently elicited in the superficial cysts Unequal consistence of the tumor, some portions elastic and other parts firm and knobbed, is an important distinctive feature A simple fibroadenoma may be found concomitantly in the opposite breast or in the same breast with the cystosarcoma phylloides (Birkett) Semb reported an instance in which multiple cystosarcomas developed about as many multiple fibroadenomas The axillary lymph nodes are not involved in the disease process, but they may become enlarged by inflamma-

tory changes when ulceration and infection occur in the breast tumor

Size

In Finsterer's series of 18 cases, 4 of the tumors were as large as a man's head. In our collective series 18 of the tumors were said to be as large or larger than a human head. The actual weight of 19 tumors was given averaging 7 6 lbs each These tumors are usually larger than a closed fist and may weigh as much as 20 kg (Ribbert) When the tumor attains a great size, the major portion of the growth has taken place in one year Some may be small for long periods

Changes in the Skin of the Breast

In Finsterer's 18 patients the skin was adherent to 4 of the tumors and ulceration had occurred in 3 instances In our collective series the status of the skin was mentioned in 65 case reports Twenty-one had ulcerated lesions at the time of examination 4 of these ulcerations were attributed to trauma. Five other tumors were adherent to the skin. In the remaining 39 patients the skin was not ulcerated or adherent to the tumor In 5 patients rapid fungation occurred once the skin had ruptured, in 1 instance an enormous cauliflower growth extruded within twelve hours time. The capsule of the tumor and the superjacent skin may be ruptured by pressure necrosis induced by tension. The fungations which frequently result are not indicative of malignancy The ulceration occurs at the lowest part of the tumor or at the point of greatest tension. Infection inevitably follows ulceration, and at times gangrene ensues Prior to rupture the skin is usually tense, smooth, shiny and dry and red, livid, cyanotic, or violaceous. Enormous subcutaneous veins, often as thick as pencils may radiate from the superficial vascular part of the tumor like a caput Medusae

Nipple

Retraction of the nipple is so very unusual that when it does occur the examiner suspects carcinoma rather than cystosarcoma. Poulsen emphatically declares that the nipple is never involved. In our collective series there was only one instance in which the nipple was retracted by a tumor in another case the nipple was obliterated.

Precursory Tumor

In 57 of our collected case reports definite mention was made of a precursory tumor Forty seven of these patients gave a definite history of the presence of a precursory tumor in the breast. In 10 instances a specific statement was made that no preexisting tumor had been present according to the patient's knowledge.

Duration

In Frangenheim's report the period of development averaged 35 to 48 months In our collected series there were 75 patients who gave this information We found the average duration to be 6 7 years from the day of discovery to the date of examination When these tumors exist for many years, they may remain inactive for a considerable portion of that time.

Rate of Growth

Finsterer found cystosarcomas and true sarcomas to develop more slowly than carcinoma of the breast. The period between discovery and examination for these three types of tumors was given as

follows 25 5 months for cystosarcomas, 18 3 months for true sarcoma, and 16 3 for carcinoma True sarcoma of the breast was said to grow more rapidly than cystosarcoma Helmuth in 1871 was the first to observe that cystosarcoma phylloides grew with extreme rapidity, with long intervals of arrested growth The rate of growth was indicated in 82 of our collected case reports In 9 patients the tumor was of slow growth, in 8 cases the tumor grew at a moderate rate, in 1 instance the growth was slow with a moderately increased rate later, in 26 cases the tempo of growth was very rapid, in 38 patients the tumors grew slowly or not at all for a long time and then exhibited sudden exacerbation of growth In 27 of these 38 case reports in which the actual time of the increased growth rate was mentioned, the average total duration of the tumor was 8 9 years, but the average time during which the tumor had shown the characteristically increased acceleration of growth was only 8 months

CYSTOSARCOMA PHYLLOIDES A BENIGN TUMOR?

The average cystosarcoma phylloides is not a true sarcoma because it does not have a sarcomatous structure consistently, it does not metastasize commonly to viscera, and it seldom recurs locally Wulfing classifies this tumor as an entity somewhere between true sarcoma and simple fibroadenoma, he admits, however, that genuine and destructive sarcoma can develop in these tumors, although it is commonly the sarcoid type Grohe made the statement that cystosarcoma phylloides is as far removed from carcinoma as is condyloma of the penis Schimmelbusch, Beneke, and Haeckel emphasize the benign nature of cystosarcoma

When the tumor perforates the skin, it gives a false appearance of malignancy The age of the patient, the rate of growth, the presence of pain, and the occasional enlargement of the axillary lymph nodes do not necessarily indicate a malignant neoplasm Enlarged axillary lymph nodes may be inflammatory

It does seem, however, that sarcoma originates in cystosarcoma phylloides more frequently than it does in the original fibroadenoma. Billroth reported two cystosarcomas which metastasized, however, there was sufficient microscopic description of these tumors to rule out genuine sarcomas Theile's case report of cystosarcoma phylloides mammae is unusual, for although histologically verified sarcomatous metastases to bone occurred, sarcoma was not demonstrated in the primary breast tumor Poulsen found that metastasis from true sarcoma of the breast occurred in 40 per cent of patients but observed recurrence or metastasis in only 25 per cent of mammary cystosarcomas of all types

Prym removed a large breast tumor and, after microscopic study in which no malignant areas were seen, diagnosed the tumor as cystosarcoma myxomatosum phylloides Two peculiar areas were seen, one of cholesteatoma and another of peculiar fat lobules in the center of the original tumor, said to have been composed of immature lipoblasts. The tumor recurred locally and then metastasized to the lungs The pulmonary metastases contained no epithelial elements Prym described the metastases as myxosarcomatous, but in his accompanying microphotographs the appearance suggests liposarcoma as well as myxosarcoma

Of 77 cases reported by Treves and Sunderland, 47 were classified benign, 18 as malignant, and 19 as borderline Nine of the malignant tumors of their series metastasized and in 8 cases caused the death of the patient Metastases usually occurred by way of the blood stream, and distant metastases presented a sarcomatous histologic structure Metastases to regional lymph nodes occurred in 1 pa-

tient. Lester and Stout, utilizing the same criteria as Sunderland and Treves classified their 58 patients as follows 20 histologically malignant, 10 borderline, and 28 benign. Lester and Stout were somewhat startled by the observation that 1 of the tumors diagnosed as being benign by histologic criteria and 2 diagnosed as borderline produced distant metastases. They thus focus upon the inadequacy of histologic classification of the degree of malignancy of cystosarcoma phylloides Of the 26 patients operated upon over five years ago 15 are well and free of disease from five to thirty years Five of these were histologically malignant and 5 of borderline malignancy

Of 91 cases in our collected series in which the outcome was mentioned, there were but 6 recurrences 1 patient died from pulmonary metastases after a simple mastectomy in 3 patients simple mastectomies were followed by recurrences which were excised, in 1 patient a recurrence followed a radical mastectomy and in another a local excision of the tumor was followed by a recurrence which was removed by simple mastectomy

DIFFERENTIAL DIAGNOSIS

Hemisection of the surgical specimen in the operating room reveals a gross appearance which is absolutely diagnostic and cannot be confused with any other tumor of the breast. The intracystic polypoid lobulations with narrow tortuous clefts are not simulated by any other tumor except the intracanalicular fibroadenoma.

The clinical differentiation from carcinoma is not difficult. No cancer could grow so large without involving the skin. The encapsulation of the tumor the freedom of the nipple the lack of fixation, and other evidences of infiltration are important diagnostic features The mobility of the skin over the tumor and the absence of the orange-peel type of skin and of regional distant metastases, as well as the maintenance of good general health, are diagnostic points in which cystosarcoma phylloides differs from cancer The three varieties of breast cancer which bear a faint resemblance to this tumor are the diffuse ductal carcinoma, the bulky adenocarcinoma, and the intracystic papillary carcinoma In the first mentioned carcinoma the breast is diffusely invaded, the tumor margins are not easily definable, the nipple is invariably retracted, and the skin of the entire breast is thickened and edematous The bulky adenocarcinoma, which occurs more often in elderly subjects, metastasizes late and often invades and ulcerates the skin it may closely resemble cystosarcoma phylloides The intracystic papillary carcinoma originating in cysts or dilated ducts is often preceded or accompanied by a sanguineous discharge from the nipple. It is occasionally multiple and once its capsule is ruptured has the ability to infiltrate

The carcinosarcoma of the breast is sometimes referred to as *adenosarcoma* Many of these tumors are enormous they may weigh from 10 to 20 lbs They often ulcerate through the skin, and the epithelial elements may metastasize to the axillary lymph nodes The round-cell sarcoma of the breast, including the lymphosarcoma, is softer than cystosarcoma, grows with greater rapidity and is many times more radiosensitive when subjected to the therapeutic test of irradiation.

The mixed tumors of the breast according to Wilms, are of teratoid origin, developing from embryonal ectoderm and *mesenchyme* which are included in the mammary gland. These tumors may contain epidermis, cartilage, and other structures indicating their origin from multiple germinal layers. Others say the mixed tumor is a metaplastic derivative of a benign tumor in this sense there may be a histogenetic relation to cysto-

sarcoma Clinically they cannot be distinguished from encapsulated benign tumors of the breast such as large fibroadenomas, adenomas, and cystosarcoma phylloides They are usually well-delimited, encapsulated tumors, which remain small for a long time and then grow with great rapidity They cause atrophy of the mammary gland proper without invasion They do not adhere to the deep tissues nor do they metastasize by lymphatic vessels They elevate and render the skin tense but never directly infiltrate the skin They occur at all ages from 20 to 70 years

An analogy exists between fibroadenomas, cystosarcoma phylloides, and chronic cystic mastitis because they have the same elementary or primary changes occurring histologically They are differentiated by delimitation (cystosarcoma and fibroadenoma) and by proliferation of epithelial tissue (fibroadenoma) and of connective tissue (cystosarcoma phylloides) Chronic cystic mastitis is a more diffuse process and has few of the clinical features of a giant intracanalicular myxoma such as the rate of growth and bulky size Tuberculous mastitis and mammary actinomycosis may be ruled out by the clinical history, by the physical findings upon examination, and finally by an aspiration of the fluid content followed by microscopic diagnosis

PROGNOSIS

The prognosis is usually good It depends on· the type of cystosarcoma phylloides, *i e*, whether cellular or myxomatous, the fixity of the tumor, the extent of the operation, the age and physical status of the patient, the presence of ulceration and infection, the duration and the size or local extent of the tumor Malignant cystosarcoma phylloides offers a poorer prognosis in view of the fact that 44 per cent of 18 such patients have succumbed (Treves and Sunderland)

TREATMENT

The management par excellence is the prophylactic measure of removing all mammary fibroadenomas If the tumors are small, local wide extirpation may be sufficient If the tumor is incompletely removed, it will recur Billroth found that cystosarcoma phylloides in young women does not recur after removal, but in older women (over 30) he advises a more radical operation because of the danger of recurrence or of even transition of carcinoma Such recurrences may be from residual portions of previous tumors or by the formation of new tumors Hence, it seems wiser in all cystosarcomas of considerable size to do a complete amputation of the breast, including the fascia over the pectoral muscles Because some may be potentially malignant, a mastectomy (occasionally radical) is the procedure of choice

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EMBRYONAL ADENOMYOSARCOMA OF THE KIDNEY (WILMS'S TUMOR)

The embryonal renal neoplasms occurring in infancy and childhood constitute a heterogeneous but closely related group of tumors Histologically and histogenetically they are not identical All intermediate varieties are found, from the type containing muscle fibers, described by Cohnheim, to a tumor which is mostly glandular In 1828 Gardner presented the first case report of a renal sarcoma occurring in infancy Eberth first accurately described this tumor in 1872 Other authors whose names are associated with the discovery and early descriptions of this disease are Cohnheim in 1875, Sturm in 1875, Weigert in 1876, Landsberger in 1877, Osler in 1879, Huber-Gostroem in 1879, Brosin in 1884, Paul in 1886, and Doederlein in 1894 In 1899 Wilms wrote his

classic monograph on mixed tumors of the kidney This neoplasm has since borne the eponym of *Wilms s tumor* The term *embryonal adenosarcoma of the kidney* was first employed by Birch Hirschfeld.

INCIDENCE

In an early study of the incidence of various neoplastic diseases which were accepted for diagnosis and treatment at the Memorial Hospital, 16,565 were malignant (Pack and LeFevre) The embryonal adenomyosarcomas of the kidney reported in this study constituted 0 083 per cent of all malignant tumors treated during this time

One feature common to tumors in children is that the localities in which they originate are different from those affected by neoplasms in adults For example, the great proclivity of infants and children to malignant tumors of the kidney and eye is in marked contrast to the rarity of tumors of these organs in adults Renal tumors of infancy and childhood practically all take origin in the parenchyma rather than in the pelvis Warner has given the ratio of occurrence of renal tumor to tumors in general in children as 20.5 per cent, whereas the ratio of renal tumors to all other tumors in adults is only 0.5 per cent. Unquestionably Wilms s tumors are the most common malignant neoplasms of the genitourinary tract in childhood.

SEX

Males and females are equally represented in keeping with the congenital origin of the disease.

AGE

The embryonal adenomyosarcoma of the kidney is a tumor peculiar to infancy and childhood It occurred at the earliest average age among 100 different histologic and regional varieties of tumors studied at the Memorial Hospital. The average age of the patients in this series at the time the tumor was first noticed was 5.3 years Excluding 1 adult from this group the average age of 15 children was 3 years The average age of Wilms s patients was 3 years In Wilms s youngest patient the tumor was discovered at the age of 1 month. Geddings Landsberger, and H. Kastner have reported instances of this disease in the 7 month fetus Wentworth, Weigert, Gairdner Jacobi Kocher Monti Tuttle, and Paul discovered embryonal renal adenosarcomas in newborn infants some of whom were stillborn

These patients with Wilms s sarcoma constituted 2.19 per cent of all subjects under 25 years of age having malignant tumors Fraser reviewed the records of 85,000 sick children in Edinburgh and stated that he had never encountered a *Wilms s* tumor at a later age than 7 years Steffen analyzed 213 cases from the literature of these, 203 occurred during the first 7 years. Albarran and Imbert found 152 of 165 cases occurring in the first 7 years

At the time of Wilms s thesis (1899) the oldest patient whose case had been reported was 18 years of age (Holsholt) Kocher and Langhaus diagnosed an embryonal renal adenosarcoma in a subject of 35 Jenckel observed the tumor in a patient of 43 Kilbane and Lester reported the case of a man aged 48, and Busse described a Wilms s tumor in a man of 57 Our oldest patient was a man of 37 when the tumor was discovered.

GENESIS

The following theories concerning the origin of Wilms s tumors have been submitted (1) origin from aberrant germ plasm (Cohnheim Ribbert, and Brock) (2) origin from wolffian body (Eberth, Doederlein, and Birch-Hirschfeld) (3)

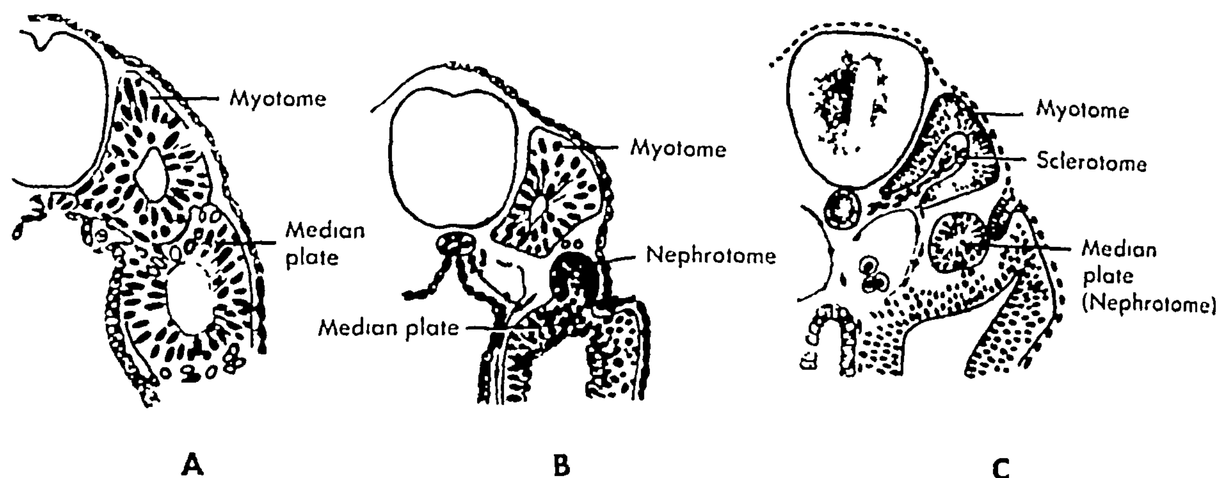


FIG 151 The origin of the kidney The contiguity of the myotome, sclerotome, and mesenchyme with the nephrotome assists in the explanation of the origin of the various tissues within the Wilms's tumor It seems probable that the tumor anlage establishes its identity at an earlier period than represented in these figures *A* Fifth primary segment of a human embryo with 13 primary segments (transverse section) *B* Tenth primary segment of a human embryo The myotome is farther distant from the lateral plate but is still connected with it by the median plate or the nephrotome *C* Section of a primitive segment from the posterior end of a human embryo 3 weeks old (Reduced from a drawing with a magnification of 240 diameters) (*After* Max Wilms *Die Mischgeschwulste der Niere*, Leipzig, Arthur Georgie, 1899, vol 1, pp 1–90)

origin from renal blastema or nephrotome (Weigert, Cornil and Ranvier, Paul, Muus, Busse, Wilms, Fraser, and Ewing), and (4) origin from endothelium (Brosin).

Cohnheim's conception of the genesis of the tumor implied an origin from aberrant germ plasm of the primordial segments Because the anlagen are so closely related to the muscles of the posterior abdominal wall, myoblasts from these muscles were thought to be included in the tumor and later became differentiated into striated muscle fibers Ribbert emphasized the presence of all three germ layers in the anlagen of these tumors and assumed the origin to be from an aberrant sex cell Brock stated that the matrix of the tumor was an embryonal germ which had been left over at the time of development of the urogenital system

Eberth ascribed the origin of renal adenosarcomas to the wolffian body He explained the presence of striated muscle fibers in the tumor as due to metaplasia of smooth muscle normally present in the wolffian body Birch-Hirschfeld attributed the glandular structures of the tumor to residual wolffian tubules Doederlein believed that the epithelial and connective tissue in the tumor were of separate origin and that the entire tumor originated from the wolffian body So far as we have been able to ascertain, no wolffian remnants have even been found in the human kidney Therefore, we prefer to discard this theory as untenable

Weigert observed multiple small adenosarcomas of the renal cortex He attributed these tumors to anlagen from the first solid ureteral branches of the kidney Cornil and Ranvier also believed in the close genetic relationship between urinary canals and this embryonal tumor Paul agreed with these writers that the tumors originated by incomplete differentiation of embryonal renal tissue, he referred to them as teratomas Busse found the prototype of the Wilms's tumor in the embryonal kidney.

Muus noted the histologic resemblance of the embryonal kidney to the renal adenosarcoma. In the human embryo of from 3 to 4 cm, the ureteral branches are surrounded by tissues which simulate the microscopic appear-

ance of these tumors According to Muus, the portion of the renal blastema which becomes delimited as the anlage of the tumor undergoes proliferation at some time in fetal life, while the kidney proper continues its normal development. The size of this tumor anlage varies in different patients

Wilms also believed that these tumors originate from the renal blastema. He stated that renal adenosarcomas develop from the region of the middle plate or nephrotome. Therefore, they may contain mixtures of cells from neighboring structures such as mesenchyme, myotome, and sclerotome. This accounts for the occasional findings of fat cartilage and muscle Fat, cartilage and elastic and mucous tissue in these tumors originate from the mesenchyme near the nephrotome or middle plate. The myotomes alone do not usually form congenital tumors in this region since rhabdomyomas of the kidneys are rare. The striated and smooth muscle fibers in the tumor do not originate from inclusions of primitive muscle cells but rather from undifferentiated germinal tissue which precedes the appearance of muscle. The predominant cell of the tumor is round, primitive, and undifferentiated and, after dividing repeatedly differentiates into the various structures which characterize the tumor such as the sarcomatous elements and the epithelial tubules. Aggregations of these round cells clump to form sarcomatous nests in the center of which the tubules later appear The glandular tissue is therefore not a primary element.

Our own conception of the origin of these embryonal renal adenomyosarcomas is presented here in summary As the tumors may vary markedly in the degree of differentiation of their component cells and in the number of tissues represented, it is evident that they originate at different developmental periods of the embryo The renal blastema or nephrotome is the predominant contributing structure. A tumor anlage which establishes its identity at this stage will elaborate tissue easily recognized as renal in origin. Such a tumor will reproduce primitive renal tubules even glomeruli may be primitively patterned. The microscopic appearance of such a tumor resembles the cortical hyperplasia seen in the "spotted kidneys" of children. In the latter condition there are numerous discrete foci of hyperplastic embryonal glomeruli and tubules

If the tumor anlage separates earlier before the urogenital ridge has formed the nephrotome, which is the definite precursor of the kidney the tumor cells have still greater possibilities for elaborating multiple tissues This multipotency may account for the presence of muscle fibers and other tissues in the tumor We believe that the smooth and striated muscle fibers the occasional fat and cartilage cells and the sarcomatous and tubular elements are all derived from primitive germinal tissues In other words the striated muscle cells are not inclusion in the tumor from the adjacent myotome, but rather they develop from a cell which is the parent of the nephrotome and myotome as well. We believe that metaplasia of smooth muscle into striated muscle is a possibility (E. J Carey has accomplished this in experiments with muscle from the ureter) but we do not believe that it is the probable explanation in the case of renal adenorhabdomyosarcomas

GROSS PATHOLOGIC ANATOMY

Embryonal adenomyosarcomas of the kidney are usually unilateral. In Wilms's collected series 7.2 per cent of the patients had bilateral tumors Kretschmer and Hibbs in a series of 17 cases found bilateral occurrence twice, an incidence of 12 per cent. In youth, when the paired organs are involved by neoplasms, bilateral occurrence is not in

frequent, whether in the kidney, eye, or ovary The question arises whether such tumors are of multicentric origin, that is, are the neoplasms primary in each kidney or is there a metastasis in one kidney from the primary tumor of the opposite side? The latter is improbable because of the manner in which these tumors spread Weigert described multiple small embryonal adenosarcomas in the cortices of both kidneys in a stillborn child All the tumors in our series were unilateral

The growth is situated retroperitoneally, displacing the colon forward and mesially On the right side it may press against the duodenum and cause obstruction These neoplasms may weigh as much as 5,000 gm The entire abdomen may be filled These tumors reach such tremendous size because they possess great growth capacity and because diagnosis is often delayed

The tumor is usually bluish and smooth The surface may be knobbed or irregularly lobulated, especially in the advanced stages On section the substance is greyish white or yellow and appears soft, medullary, fibrous, gelatinous, vascular, or edematous Various pathologists have described this neoplasm as *in* the kidney and *of* the kidney and have emphasized its encapsulation. There is apparently a complete separation from the renal parenchyma Very few extrarenal tumors of this type have been reported, among them are the cases of Brock and Vogler

Wilms's tumors may occur in any part of the kidney, in either pole or in the center, although usually the lower half of the organ is involved, in contrast to the tumor of Grawitz in the adult. The growth is always located within the renal capsule unless the capsule has ruptured, in which event the neoplasm develops along the route of least resistance The tumor frequently extends toward the renal pelvis and may push residual kidney substances before it to form a pseudopolyp The tumor frequently protrudes from the kidney at the hilus The preserved portion of the kidney may maintain its natural configuration, but the form is changed, it may resemble a cap which fits on the tumor The wall of the renal pelvis adjoining the surface of the tumor is either adherent to it or separated by a layer of connective tissue of variable thickness

PATHOLOGIC HISTOLOGY

Wilms's tumors are composed entirely of tissues of mesodermal origin In some specimens the predominant cells are round, hyperchromatic, and undifferentiated In other cases the differentiation is more complete, and one is able to see abortive attempts at the reproduction of tubules and glomeruli Interspersed among these structures from the renal blastema proper are other tissues, such as smooth muscle, striated muscle, myxomatous tissue, and, rarely, cartilage and fat

The epithelial elements in the tumor consist of tubules of different sizes and shapes lined by cylindric or cuboidal cells The basement membrane is often imperceptible The glandlike tubules are usually single-layered and have a tendency here and there to form cysts In certain regions the epithelial tissues may form solid cords or strands Abundant mitoses in the cells of these tubules indicate their activity in the histogenesis of the tumor

The round or polygonal cells with hyperchromatic nuclei are presumably undifferentiated They may elaborate either rudimentary tubules or possibly sarcomatous stroma, muscle, and fat Occasionally one may observe groups of cells which are epidermoid in appearance These are interpreted as metaplasia The round, undifferentiated cells may also subdivide into other forms, some of which are elongated and anastomosing and possess rod-shaped nuclei

Striated-muscle fibers are not fre-

quently found in Wilms's tumors The muscle cells contain several nuclei and may have transverse striations In size they correspond to the muscle fibers in a 7 month fetus (Busse) These striped muscle fibers are arranged in fasciculi parallel to one another and interlacing No sarcolemma is distinguishable Some of the cells are long, pointed, and spindle-shaped with a rod shaped nucleus similar to that of the smooth muscle cell but with early cross-striations beginning near the nucleus Ribbert asserted emphatically that these striated muscle fibers develop by metaplasia from smooth muscle. In this he was supported by Busse Smooth muscle fibers are seen in these tumors somewhat more frequently than striated muscle fibers The renal capsule and the wall of the renal pelvis normally contain networks of smooth muscle fibers, but it is unlikely that these elements contribute to the formation of muscle tissue in the tumor The manner of growth of the tumor and its complete encapsulation within the kidney would indicate that the anlage of the tumor originated prior to the organic identity of the kidney

The capillaries in the tumor do not have time to grow into thick walled vessels. They remain fragile and bleed easily This accounts for the frequent hemorrhages into the tumor Other structures such as fat and myxomatous tissue, are not prominent components of the tumor substance but are present in a sufficient number of cases to justify the use of the term *mixed tumor*

SYMPTOMATOLOGY AND PHYSICAL SIGNS

The sequence of events in the clinical history of a patient with an embryonal renal adenomyosarcoma is usually as follows

1 Gradual and progressive abdominal distention
2 Increasing malaise and constipation

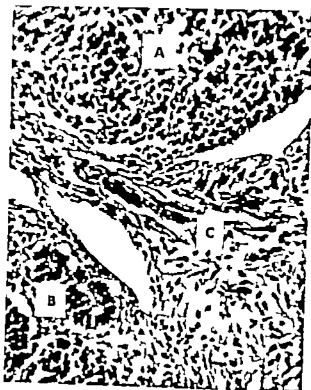


FIG. 152. Wilms's embryonal adenomyosarcoma of the kidney *A.* Undifferentiated epithelial masses. *B* Abortive tubule formation *C* Muscular elements.

3 Discovery of the tumor (usually accidental)
4. A sudden augmentation of symptoms, such as vomiting, loss of weight, asthenia, anorexia, increased rate of tumor growth, and the appearance of tortuous dilated, superficial veins
5 Still later possibly ascites, marked emaciation, enormous enlargement of the abdomen, and metastases
6 Death by cachexia or intercurrent disease

The first symptoms of illness in our patients were given as follows (1) the sudden discovery of a mass in the abdomen (50 per cent) (2) onset of pain (25 per cent) (3) asthenia and malaise (12.5 per cent) (4) hematuria (6.25 per cent) and (5) frequency of urination (6.25 per cent)

As the condition of the child during the earliest stages of the disease is not abnormal, the diagnosis is seldom made until the growth is of considerable size. Usually the tumor is discovered accidentally by the parents, more rarely in the course of a general physical exam-



Fig 153 Wilms's tumor of the left kidney in an otherwise apparently normal infant

ination Palpation of a mass is the most frequent and important sign

When a child with Wilms's tumor is examined, there are six important features which may be ascertained by careful palpation, namely, location, size, surface configuration, consistency, flexibility, and tenderness of the tumor to pressure Tenderness may not be present, and there is usually no muscle spasm over the tumor Inspection and percussion of the abdomen are helpful Ballottement enables the examiner to determine the retroperitoneal position of the tumor There may be a fullness at the costovertebral angle A palpable tumor is a most significant observation in either a child or an adult, but in a child it is of the greatest importance because it may be the only diagnostic sign The tumor may not be felt in children because of their adiposity Also, in young children the kidney normally lies deeper in the pelvis than it does in adults, extending as low as the crest of the ilium

The surface of the tumor usually feels smooth, although it may be lobulated in later stages When necrosis or hemorrhage occurs into its substance, the tumor may be soft and seem fluctuant, simulating the consistency of hydronephrosis Flexibility of the tumor depends on the space available for movement within the abdomen Primary tumors are seldom adherent and frequently move with respiration The connective-tissue capsule which separates the tumor from the kidney may form a groove, deep enough at times to be palpable through the abdominal wall On the left side such a groove may simulate the notch in the margin of the spleen The neoplasm may extend to the midline

Hematuria is usually due to hemorrhage from the parenchyma of the congested kidney rather than from the tumor itself It may occur in the early stages of tumor growth before the calyces of the renal pelvis are completely atrophied and compressed There is little danger of a fatal hemorrhage, although death may follow hemorrhage if the patient is moribund The blood is usually diffused throughout the urine Occasionally blood casts of the ureter have been detected. Hematuria occurs only at irregular intervals In adults it occurs in from 75 to 85 per cent of patients with renal tumors In children hematuria is relatively infrequent. Only from 10 to 25 per cent have been reported as showing this symptom. Of course, there is a great difference in the renal tumors from which adults and children most commonly suffer Five of the patients from our series had transient hematuria Gross hematuria seems to indicate a bad prognosis, not from the hemorrhage per se but as an expression of the diffuse growth of the sarcoma

Pain is not an important feature of the symptomatology of Wilms's tumors. It may be colicky as the result of constipation, or it may occur when the tumor grows very rapidly and exerts tension on the renal capsule and possibly traction

on adjacent organs In babies this pain is difficult to evaluate. Indeed, the "silent" nature of this tumor is remarkable. The neoplasm is not tender to palpation. Half of the patients in this series suffered some degree of pain at certain stages of the disease. The pain was usually transient. Because of the enormous size of the tumor in some cases the child may be able to walk only with great difficulty

Urinary signs are usually insignificant and unimportant. Probably this is because the tumor is separated by its capsule from the kidney parenchyma. Normal urine may be found on many examinations because the diseased kidney does not function on account of pressure atrophy and destruction Erythrocytes are sometimes seen on microscopic examination Urinalysis may be of some aid in detecting the onset of inflammatory complications One diagnostic sign of value is the appearance of albuminuria following pressure on the tumor

Recurrent tumors following nephrectomy often provoke difficulties in urination because they usually develop in the pelvis and compress the bladder In 40 per cent of our patients with recurrent tumors some urinary signs such as nocturia, dysuria, polyuria, and urgency were present. Pyelograms may show marked or complete kidney dysfunction

Fever is frequent in these patients as it is in other children who have malignant neoplasms, such as lymphosarcoma and endothelial myeloma. Fever may be the first and only symptom. Occasionally it is associated with hematuria. It may be a terminal complication Sixty per cent of the patients studied in the authors series had fever ranging from 101.5° to 104.0° F It was always intermittent In our experience fever was not related to the stage of the disease.

Hypertension a rare finding in infancy has been recorded with sufficient frequency in children with Wilms's tumors to suggest a causal relationship and a finding that might aid in establishing the diagnosis



Fig. 154. Intravenous pyelogram of a 5-year-old girl bearing a large Wilms's tumor of the left kidney which was successfully excised and treated with postoperative deep x ray therapy Note complete lack of function of left kidney

Edema of the lower extremities is a late sign caused by pressure on the iliac veins

Other signs and symptoms are loss of weight, asthenia, malaise, anorexia, insomnia, anemia petechiae of the skin, and late digestive disturbances In four of our patients ascites developed in the terminal period of the disease. Two other children had enormously dilated and tortuous superficial veins over the abdomen on the side of the tumor

DIFFERENTIAL DIAGNOSIS

The clinical features of a large, rapidly growing kidney tumor in a young child are usually so definite that the diagnosis is easily established by physical examination. Wilms's tumors grow so rapidly that the only hope of cure depends on early diagnosis When a large mass is palpable, the disease al

ready is advanced There are several other intraabdominal masses which might lead to confusion.

1 Lymphosarcoma of retroperitoneal lymph nodes is centrally located and is surrounded by resonant intestines In the case of a Wilms's tumor, resonance is mesial to the abdominal mass The therapeutic test by irradiation is of no aid, as the two tumors are of equal radiosensitivity Regional lymph nodes are more frequently affected by lymphosarcoma

2 Tumors of mesenteric lymph nodes —lymphosarcoma, malignant lymphogranuloma, or tabes mesenterica—are massive, somewhat superficial, and situated near the umbilicus

3. Suprarenal tumors in children may be attended by disturbances of the endocrine system Chromaffin tumors of the adrenal medulla (neurocytomas) usually reveal their presence by distant metastases—for example, in liver, bone, and orbit

4 The tuberculous kidney is seldom as large as the renal adenosarcoma Urinary signs are positive and pathognomonic

5 Hydronephrosis is quite rare in children A urologic examination should readily differentiate the two conditions

6 Polycystic disease of the kidneys is usually bilateral

7. Tuberculous peritonitis is sometimes quite difficult to differentiate from embryonal renal adenosarcoma The general physical examination, doughy consistency of the abdomen, roentgenograms of the lungs, and the family history afford sufficient criteria to establish a diagnosis if a urologist is not available

8 Hepatic tumors are somewhat rare in children. Although they are seldom accompanied by jaundice, there usually are severe gastrointestinal symptoms and pain

9 Ovarian tumors are rare in children They are usually bilateral and may be diagnosed by bimanual examination with one finger in the rectum

10 Splenomegaly is more superficial than adenosarcoma of the left kidney and is situated higher in the abdomen Examination of the blood is helpful in detecting leukemia, malaria, or syphilis

11 Pancreatic tumors are rare in children and are attended by unusually severe gastric symptoms and intractable pain

12 Fecal tumors are more superficial than renal adenosarcomas, they are freely movable and are accompanied by obstipation or intestinal obstruction The diagnosis is verified by roentgenograms of the colon

13 Psoas abscess.

One is never justified in performing a biopsy on a Wilms's tumor Excising tissue for histologic study destroys important natural barriers to tumor growth As a consequence direct extension of the neoplasm is extraordinarily rapid and widespread

The need for a biopsy should seldom arise if a thorough urologic examination is performed Intravenous pyelography may give complete information regarding the anatomic structure of each kidney and its function, but if not, cystoscopy should be done together with ureteral catheterization, functional tests, and retrograde pyelography Pyelograms seldom show a deformity of the renal pelvis that is characteristic or specifically diagnostic of the Wilms's tumor One important value of pyelography, however, is to ascertain the presence of a normal opposite kidney Age is no contraindication to the use of the cystoscope in either sex It is essential to know the functional capacity of the sound kidney before any type of treatment is undertaken, and since the incidence of congenital malformations is unusually high in patients with Wilms's tumors, it is equally important to know what anatomic conditions exist before beginning an operation.

METASTASES FROM WILMS S ADENOMYOSARCOMA

Embryonal renal adenomyosarcomas usually progress by direct infiltration. The omentum and nearby organs of the peritoneal cavity are invaded first. A number of bizarre cases illustrating the remarkable invasive qualities of this tumor have been recorded. All the abdominal viscera may be affected. The walls of blood vessels especially veins and the ureter have been destroyed. Even the diaphragm offers slight obstruction to the progress of the growth.

True venous metastases may occur or extension may follow lymph channels The veins within the tumor are large and fragile. They frequently rupture spontaneously and are sometimes invaded by tumor cells The growth in a vein may develop until it reaches the renal vein and ultimately the vena cava. On record is one case in which the tumor extended in unbroken continuity from the kidney to the right side of the heart. Osler described the sudden death of a patient from the blocking of the tricuspid valve by a sarcomatous thrombus which had been dislodged from the renal vein. Or metastasis may occur by direct extension through the enveloping capsule. Lymann states that 50 per cent of the embryonal renal adenomyosarcomas metastasize to other organs Wilms s figure for this complication was 30 per cent. In our series 30 per cent of *patients had metastases to lymph nodes* (retroperitoneal, mediastinal, and inguinal groups) Metastases occurred also to the liver lungs, bones, and the corpora cavernosa.

PROGNOSIS OF WILMS S ADENOMYOSARCOMA

As with any tumor the possibilities of cure or palliation are greater for primary than for recurrent growths. Firm solid tumors offer a better prognosis than lobulated, fluctuant neoplasms because *the former remain longer within their* capsules Three-fourths of the postoperative recurrences develop within the first year (Salleras) but even by the *fourth postoperative month the majority* of residual tumors have demonstrated their recurrent growth. About 50 per cent of children with this form of sarcoma can be cured. Children with this tumor have less resistance to intercurrent diseases than adults Unfortunately correlated studies in laboratories of pathology have shown that the prognosis for the child patient or the extension of the growth has no demonstrable relationship to the types of cellular structures predominant in the neoplasm These variations in structure have academic rather than clinical importance

TREATMENT OF RENAL ADENOMYOSARCOMA

Radiosensitivity of Wilms s Tumor

The radiosensitivity of the renal adenomyosarcoma is dependent on several factors (1) congenital origin (2) embryonal structure (3) unstable vascularity The widely distended capillaries and venules of the tumor have thin walls. Radiation destroys these vessels and induces bulky ischemic necrosis (4) rapid cell division, demonstrated by the large number of mitotic figures (5) the high rate of metabolism of the tumor cells (6) the anatomic character of the cells (nuclear hyperchromatism, nucleocytoplasmic ratio, etc.)

Radiation Therapy

In earlier years nephrectomy for Wilms s tumors was usually performed through a posterolumbar incision, with the deplorable result that (1) local recurrences were common (2) distant metastases commonly appeared later (3) the operative mortality was high,

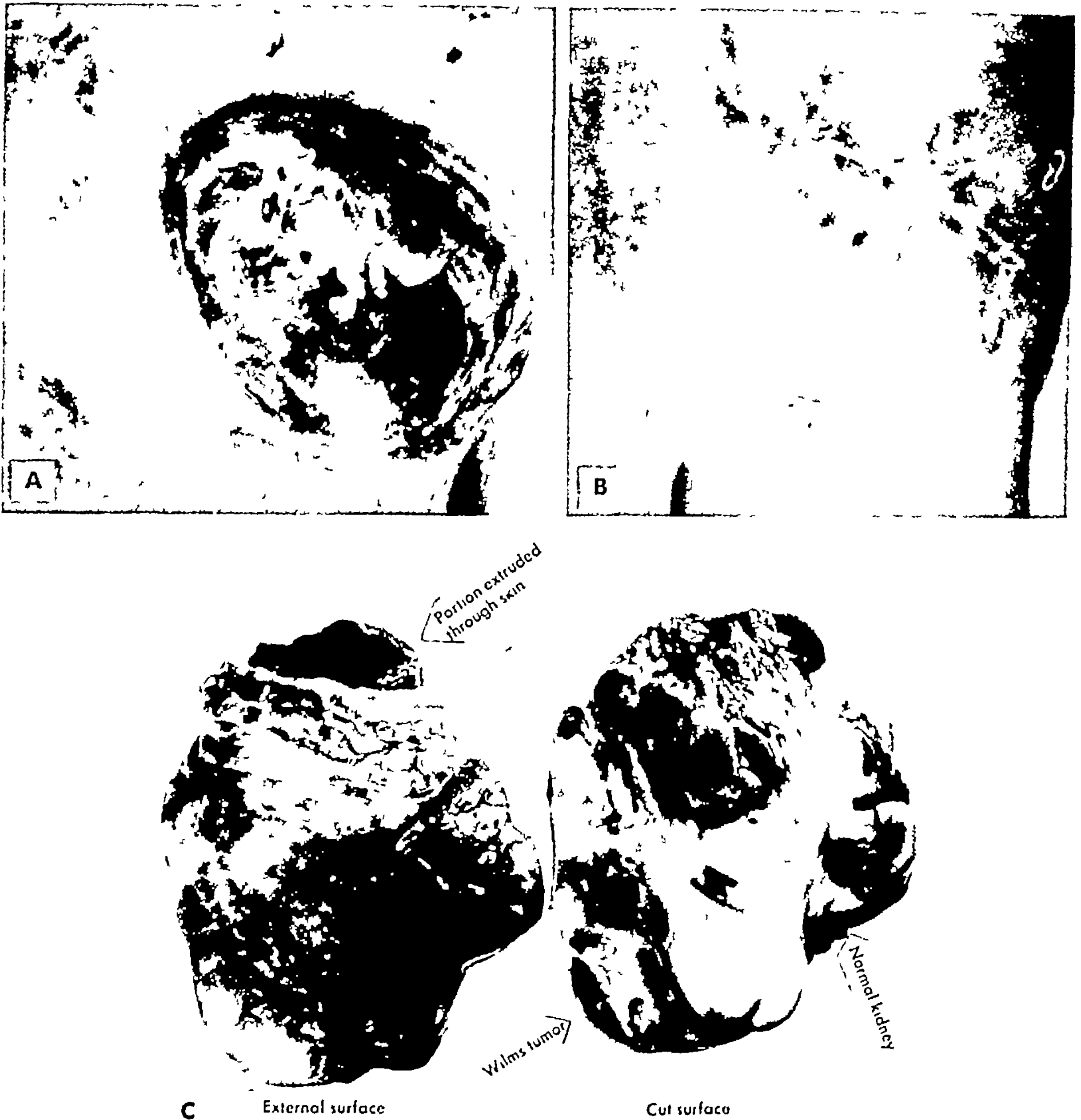


FIG 155 A huge recurring Wilms's adenomyosarcoma of the kidney in a female child It had extended to protrude through the skin *A* Clinical photograph illustrating the protrusion of an adenomyosarcoma through the abdominal wall. *B* Clinical photograph after a radical surgical extirpation of the neoplasm *C* The surgical specimen, demonstrating the extent of the neoplasm and its effect upon the contiguous structures

and (4) the results achieved were usually palliative Also, many tumors were technically inoperable through this exposure These facts, together with the known phenomenal radiosensitivity of the tumor, conspired to furnish the imperative indications for preoperative irradiation Indeed, we so advocated the routine application of this measure in an essay published twenty years ago Now that the surgical difficulties have largely been surmounted, the indications for irradiation seem limited to four conditions (1) a huge, fixed tumor deemed technically inoperable when first seen may become technically resectable after preliminary x-ray therapy, (2) postoperative x-ray therapy wl
is invasive and the ope
fident of its comple
radiation therapy alone
and recurrent inoperal
comas, and (4) irradiati

Wilms's tumors are s

cured by irradiation alone, because surgical removal following complete regression after x ray therapy has shown *viable tumor cells imprisoned* in the fibrous remnant of the lesion this accounts for the usual tardy recurrence of the sarcoma. If x ray therapy or a large radium-element pack is employed as a preoperative *measure, the surgeon usually postpones* nephrectomy for four to six weeks by which time maximal regression has occurred. If the opportunity of removing the tumor during this period of inactivity *is lost,* recurrence *is inevitable. Successive recurrences* following repeated irradiation seem to be progressively more resistant to treatment, indicating the property of this tumor of acquiring radio-resistance.

*The procedure of preoperative irra*diation has both proponents and opponents Gross reports experience whereby preoperative irradiation was given to every other patient bearing Wilms's tumor and that within *a year after this* regimen the fatality increased *so sig*nificantly that he felt the preoperative irradiation was definitely detrimental and abandoned its use.

Recurrent tumors and metastases should be treated palliatively by external irradiation alone. Under such management the patients improve greatly in general health, and the physical and radiographic evidence of the lesions may temporarily disappear It is difficult to estimate how effective irradiation is in prolonging the lives of patients with Wilms's tumors We be*lieve that the benefit is substantial.*

In applying irradiation to young children the radiologist must use great caution Each patient must be treated by preliminary exposures More inten*sive irradiation* can be given *only* when it has been learned that the patient will tolerate such treatment. Of course, adjacent organs such as the liver spleen, and opposite kidney are protected as *much as possible. Careful examinations* of the blood should be made from time to time because *these young children so easily* acquire a dangerous leukopenia. We have shown that irradiation of a Wilms's sarcoma in infancy may so interfere with osteogenesis of the dorsolumbar *vertebrae as to cause scoliosis* and *other* bony *deformities in later* childhood (Arkin Pack, Ransohoff and Simon) Retardation of long bone growth following roentgen irradiation of the epiphyses is a well recognized effect. Case report No 12 demonstrates *the subsequent development of* scoliosis in a patient whose spine had been heavily irradiated in early childhood. The isolated lumbar curve (itself a rare occurrence) exactly followed the field of radiation, and the wedging was directed toward the *irradiated side In addition* to the inhibition of growth in the left half of the vertebral bodies there was inhibition of growth in the left twelfth rib the left lumbar transverse processes *and the left ilium, all included in the* field of irradiation.

The excellent results obtained from *postoperative irradiation are epitomized* by the significant improvement in the rate of cure obtained at the Boston City *Hospital when they instituted postop*erative irradiation Postoperative irradiation is commenced usually on the day of operation if the child has tolerated the operation well. From two to *three portals are outlined over the* renal bed and fractionated irradiation utilizing cross fire technics, is employed. The factors are usually 200 to 250 kv H.V L. of 1.0 to 1 1 Cu, 200 to 250 r to one *portal each day until* a total dose of 1200 to 1750 r × 3 has *been admin*istered

Surgical Treatment

If no contraindications to immediate operation are present and the neoplasm is considered to be in the stage of operability the present conception of man

agement is to act as if the condition were an emergency If a child is discovered to have within the abdomen a large mass which is suspected of being a Wilms's tumor, intravenous pyelograms are made on the very day, almost within the hour, and the child is scheduled for operation as soon as possible—never later than 24 hours except for extraordinary extenuating circumstances

The *posterolumbar* incision for the nephrectomy has been abandoned, unfortunately many years too late Many tumors of this type were pronounced inoperable in earlier years because of apparently insurmountable technical difficulties encountered through this limited exposure The inoperability was technical rather than absolute, and the majority of such tumors today would be safely removed The posterolumbar approach required the kidney and the tumor to be handled during mobilization and before the renal pedicle was tied, thus increasing the hazard of disseminating the sarcoma cells through the renal vein

The *transperitoneal* approach is chosen because (1) it affords a wider and better exposure, (2) there is less trauma and shock incident to the operation, and (3) the renal pedicle may be ligated preliminary to mobilization and removal of the tumor A vertical incision is preferred The ascending colon (if the right kidney) and the descending colon (if the left kidney) are retracted medially, and the posterior parietal peritoneum is incised along the lumbar gutter The ureter and renal pedicle are then identified and carefully ligated and severed This precaution conserves blood in addition to its other advantages The kidney and tumor are removed with as much perirenal fat as possible, Ladd and White stress the importance of removing the fat and areolar tissues of the renal pedicle, because they contain the lymphatics in which local recurrences develop

The huge Wilms's adenomyosarcomas may be attacked more aggressively by a bold *lateral laparothoracotomy* incision, which may be safely done on either side On the right side this wide exposure enables the operator to deliver the liver into the chest and on the left side the spleen, in both cases greatly facilitating the exposure and safe removal of the neoplasm Transfusions of blood, of course, are given concurrently with the operation

If care is taken with hemostasis, the operative recovery should be reasonably prompt The young age of the patient is a handicap but not an obstacle to successful surgical treatment Burg in Hamburg operated successfully on an infant aged 12 days, and Deming at Yale performed a successful nephrectomy for Wilms's tumor on an infant 29 days old Contraindications to nephrectomy for this neoplasm are the presence of metastases, bilateral occurrence, and complete inflexibility or fixation of the tumor

The presence of tumor dissemination would influence the type of therapy to be given. The question of a palliative nephrectomy in the presence of pulmonary metastases must be adjudged in the light of clinical exigencies Excellent regression of pulmonary metastases following intensive radiation therapy to the lungs has been reported (Kerr and Silver)

END RESULTS

In previous years the operative mortality for nephrectomy and removal of Wilms's embryonal adenomyosarcomas was often as high as from 15 to 40 per cent Ladd and White *(1941)* did 23 consecutive nephrectomies for this tumor without an operative mortality They stated that a relationship appeared to exist between the age of the patient and the curability, because of 16 of their patients with the tumor occurring

in the first year of life, 50 per cent were cured.

In the discussion of the paper by Ladd and White, James T Priestley of the Mayo Clinic furnished data on end results in relation to preoperative and postoperative irradiation (1941) Nephrectomy and postoperative irradiation resulted in a cure rate of 18 per cent. Of the patients who had preoperative irradiation, 25 per cent were cured.

In 1943 a cure rate of 16 per cent of 44 patients was reported from the Mayo Clinic. Various types of therapy were employed. Dean reported from the Memorial Hospital a 25 per cent five-year survival in 20 unverified patients treated solely by irradiation. A report by Nesbit and Adams in 1946 revealed a 50 per cent five-year-cure rate of 16 patients with verified Wilms's tumor Silver reported a 55 per cent five-year survival in 18 patients

An interesting experience of 96 patients with Wilms's tumor reported by Gross revealed a rather poor survival *rate of 14 9 per cent of 27 patients* treated between 1914 and 1930, inclusive, which improved to 32.2 per cent of 31 patients treated between 1931 to 1939 inclusive. From 1940 to 1947 38 patients were treated of whom 18 were cured (47 3 per cent) This decided improvement was attributed to the utilization of postoperative irradiation The best results were obtained in patients below 12 months of age, in whom an 80 per cent five-year-cure rate was obtained this percentage decreased to 43.3 per cent for patients above 12 months of age. No reason to account for this difference could be found, and it would seem that the earlier diagnosis of an existing tumor might very well be a factor

CASE REPORT NO 12, WILMS'S EMBRYOMA OF THE KIDNEY

P N a child 5½ months old, was first seen for a huge bathing trunk nevus that occupied the entire back from hips to the shoulders and base of the neck. Superimposed upon this brown pigmented neuronevus were more than 30 coal-black, discrete elevated, smooth plaques of different texture At intervals of two months a half dozen of these plaques were excised at each operative séance until all of the suspicious lesions were removed Under microscopic study they were histologically typical of malignant melanoma but no evidence of blood or lymph vessel invasion was found. The indication for their excision in infancy was the well known tendency of these prepubertal melanomas to behave as malignant tumors after the onset of puberty

One year later at the age of 18 months, the child complained of abdominal pain of two weeks duration. A tumor was felt in the left abdomen at a point corresponding to the site of the left kidney the presumptive diagnosis was supported by radiographic study A roentgenogram of the chest revealed no evidences of pulmonary metastases A presumptive diagnosis was made of Wilms's embryoma of the kidney

Preoperative irradiation was administered *using the following factors 200 000 volts,* 0.5 mm copper filter 50 cm target skin distance size of portals 13 0 × 10.5 cm 30 ma. of current, 300 r daily exposure alternating on consecutive days. Three portals were used, *viz.*, left kidney anteriorly left kidney laterally and left kidney posteriorly A total dose of 1800 r × 3 was given The tumor regressed rapidly in size until it was barely palpable (This was done in 1936 at present the patient would not have received any *preoperative irradiation.*) Four weeks after the onset of radiation treatment, a nephrectomy was performed. The tumor was a malignant Wilms's embryoma of the kidney The kidney was largely replaced by nodular tumor which involved both poles and the intervening portion The capsule of the kidney was not perforated.

Postoperative irradiation was given using 200 000 volts 0.5 mm. copper filter 50 cm target skin distance, 3 portals of treatment, anterior posterior and lateral directed toward the bed of the left kidney with portals measuring 7.8 × 5.2 cm One hundred roentgens were administered daily

alternating until a total dose of 2000 r × 3 was given

On May 30, 1950, when the child was 15 years of age, there was no evidence of recurrence She had a marked scoliosis of the dorsolumbar spine, apparently due to radiation interference with osteogenesis on the left side of the vertebrae There were a shortening of the left leg and atrophic changes with shortening in size of the left foot Similar skeletal abnormalities have been produced experimentally in animals by Arkin and Simon

Comment

The apparent cure of the Wilms's tumor in this instance was effected through early diagnosis and immediate therapy which included nephrectomy and judicious irradiation, but the patient developed metastases to the brain from melanoma and succumbed

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SARCOMA BOTRYOIDES

Mixed tumors of mesoblastic origin occur more commonly along the urogenital tract than in other body systems Schwalbe has suggested the term *dysontogenetic tumors* as a group or generic title to include the various types One of the most interesting and rare neoplasms in this category is the so-called *sarcoma botryoides,* which usually originates from the vagina, cervix, or uterus It has been described as arising from the bladder, anus, etc This is not a tumor *sui generis,* because the botryoid or "grapelike" appearance is the result of the moisture or edema of the polypoid masses In fact, the identical tumor of exact histologic structure may be dense and dry The usual tumor is a moist, racemose, friable growth of strawberry or grape color and is endowed with prolific growth energy It arises beneath the vaginal mucosa, grows diffusely beneath the mucous membrane, ruptures through this tunic, and fungates to project into and fill up the vaginal tube, later to protrude at the vulva

Although it has been generally believed that botryoid tumors are peculiar to infancy and childhood, an increasing number of case reports attest to their occurrence in early adult life and in rare instances after the menopause The sites of origin, behavior, and prognosis of these neoplasms differ in the prepubertal and postpubertal age groups In infancy and early childhood, the vagina is the site of predilection, in later life, the cervix and corpus of the uterus are primarily involved Metastases occur rarely in infancy and childhood and more commonly when the tumor develops in adults Sarcoma botryoides would seem to be limited for anatomic reasons to females Analogs of this tumor arise in the male in the region of the prostate and extend into the bladder, pelvis, and rectum

An embryologic basis for the origin of this mixed-cell tumor coincides with Cohnheim's theory of aberrant cell and tissue rests The mullerian ducts elongate caudally, descending toward the urogenital sinus, where the approximated terminations of both cause a slight projection in the posterior wall of the sinus, named the mullerian tubercle In males, the tubes disappear except the extremities, the upper vestige being the appendix testis and the lower remnant the prostatic utricle or uterus masculinus In the female, the upper trumpet-shaped expansions become the fimbriated stomas, the central segments the fallopian tubes, and the lower parts, having received a mesenchymal investiture, become fused at the fourth month to form the uterus above and the vagina below The dislocation of cell groups, according to McFarland, and the elongations, fusions, insertions, and multiplications of these groups with admixtures and reinforcement from adjacent myotomes lead to the occasional development of this bizarre tumor The tissue elements are diverse, striated muscle cells sometimes being of such prominence as to lead the tumor to be designated as a rhabdomyosarcoma, and the other cellular components to be ignored

Approximately 50 per cent of these tumors originate on the anterior vaginal

arly invasion and destruction of sicovaginal septum are the rule, onsequent fungation into the uri ladder They may present pri in the bladder The locally in- tendency of sarcoma botryoides wed by obstruction of the urethra eters and by the complications of ion, necrosis infection, and hem e. Sepsis and urinary complica re the common causes of death.

MENT

npleto surgical removal of the and entire vaginal tube by a ned abdominal and perineal ap- i offers the only opportunity for The grapelike, bunched appear of the tumor has encouraged the practice of attempting cure by nent. Conservative surgical meas- ire followed by fatal recurrences. urinary bladder becomes invaded, radical hysterectomy total cystec and complete vaginectomy and stomy with bilateral ureterointes- anastomosis would be in order tion therapy in our experience has been curative and is of variable in effecting palliation

ickman has reported the successful ion of a huge botryoid sarcoma in ear-old girl by excising vulva, va uterus, urethra, bladder and the ramus of the pubes and by per ng a ureterosigmoidal transplant. child is well 2½ years postopera

o malignant nature of this neo- i is demonstrated by the unsuccess- ttempts at surgical ablation in 6 ren reported by Gross. One 16- h-old child reported by him is well ırs after an abdominoperineal hys- tomy bilateral oophorectomy and ectomy Of 10 cases reported from Armed Forces Institute of Pathol- 8 died from the sarcoma.

io following case report illustrates the treatment of a sarcoma botryoides in a 28-year-old female

CASE REPORT NO 13: SARCOMA BOTRYOIDES

F T a 26-year-old, single woman in good general health, related a normal men- strual history until February 1949 at which time menorrhagia occurred and persisted.



FIG. 156. Gross specimen of a soft myxo- matous sarcoma botryoides developing at the cervicovaginal junction of a 26-year-old woman. (Case report No. 13)

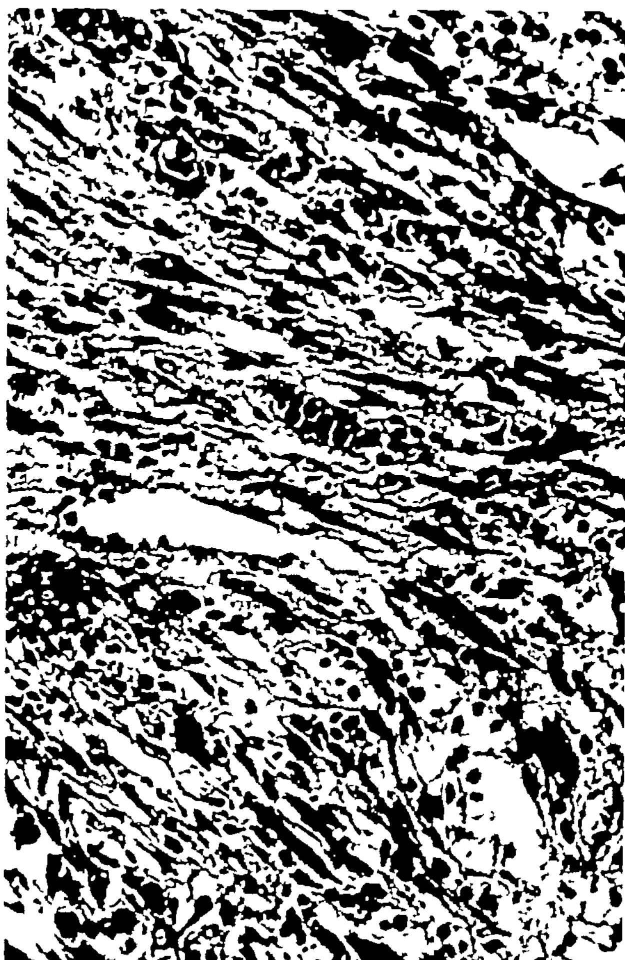


FIG 157 Photomicrograph of sarcoma botryoides (Fig 156) illustrating the bizarre neoplastic cells and myxomatous stroma



FIG 158. Higher-power photomicrograph of sarcoma botryoides shown in Figs 156 and 157, illustrating certain elongated spindle cells resembling myoblastic and polyhedral cells containing vacuolated cytoplasm

Pelvic examination revealed a huge tumor occupying the entire vaginal cavity and originating from the anterior lip of the cervix and the anterior fornix of the vagina This polypoid ulcerated tumor was soft and bled readily when touched The body of the uterus was of normal size The bladder was normal

On April 26, 1949, a total hysterectomy and partial vaginectomy was done by Dr Theodore Miller The specimen included a small nulliparous uterus, cervix, and a considerable portion of the vagina, with a huge, soft myxomatous tumor originating from the cervicovaginal junction (Fig 156)

Microscopic study revealed the polypoid neoplasm to have a myxomatous stroma in which were anaplastic cells of various types (Fig 157) Some were long and spindle cell in shape, while others were round and polyhedral and contained a vesicular cytoplasm The elongated cells resembled myoblasts which perhaps were smooth in type, but here and there was a suggestion of myofibrils Foam cells containing small hyperchromatic nuclei were seen (Fig 158)

Pathologic Diagnosis

Sarcoma botryoides of the cervicovaginal junction

End Result

The patient was examined in 1957 and was found to be free of evidence of either recurrent or metastatic sarcoma

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CHAPTER 16

Tumors of Primitive Mesenchyme

MYXOMA

DEFINITION AND NOMENCLATURE

Most tumors which arise from mesenchymal derivatives arise from cells which have matured and differentiated so that the neoplasms simulate the adult cell form Thus the cells that compose liposarcomas simulate or mimic lipoblasts, and synovial sarcomas simulate synovial cells

There are two groups of tumors which apparently arise directly from primitive mesenchyme—embryonic rests within the developed organ—and which either reproduce the characteristics of primitive mesenchyme or else develop the diverse growth potentialities of the prodromal structural cell These tumors produce cells of two or more types, such as a combination of synovial cells, lipoblasts, rhabdoblasts or other mesodermal cells The first group are termed *myxomas* to designate their histologic structure The second are called *mesenchymomas* to emphasize the growth momentum and differential capabilities of the cell of origin They are composed of cell types that are the result of the developmental routes pursued by the neoplastic proliferation of the primitive cell

Myxomas are tumors composed of primitive cells which may be multiformed but are most frequently stellate and exist in a loose stroma in which are numerous fine fibrils of reticulin coursing haphazardly throughout the section The stroma is usually diffuse like that of the primitive mesenchyme These tumors have been described by Stout as being fifth in frequency of all the tumors of the soft somatic tissues in his series. Fibrosarcomas, liposarcomas, and tumors of muscle origin (leiomyosarcomas and rhabdomyosarcomas) exceeded myxomas in frequency A great deal of confusion has existed concerning the true nature of myxomas because of the fact that other tumors of mesodermal origin, such as liposarcomas and fibrosarcomas, contain regions of myxomatous degeneration This led to such appellations as *fibromyxosarcoma* or *myxoliposarcoma* In fact, Ewing has suggested that in such instances, where the myxoid tissue composes an integral part of a tumor of another mesodermal derivative, the term *myxomatodes* should be applied, and thus fibrosarcoma with myxomatous changes should be labeled *fibrosarcoma myxomatodes*

The advisability of using the designation *myxoma* for such composite tumors is questionable It is theoretically pos-

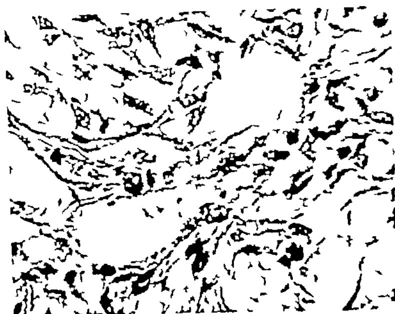


FIG. 159 Myxoma. The fibroblastic cells of this myxoma are separated from each other by the pale-staining mucoid Their cell bodies are evident, as are their processes as they lie in the homogeneous matrix.

sible that in certain regions of mesodermal tumors pure mesenchyme has remained to reproduce a region of myxomatous changes within a fibrosarcoma, liposarcoma, chondrosarcoma, or other sarcoma, but it is more probable that these foci of myxomatous changes represent regions of degeneration presenting only an appearance of myxoma

The ground substance of a true myxoma consists of a homogeneous material with a gelatinous, mucinous consistency which stains positively with mucicarmine.

The ground substance is rich in hyaluronates and in one instance cited by Stout was found to liquefy after the application of hyaluronidase. It would be important to test the effects of this enzyme upon the ground substance of those regions of myxomatous degeneration within a fibrosarcoma or some other sarcoma. This would indicate the true nature of the neoplasm whether composite or of single form with degenerative changes.

A myxoma is a true tumor arising from the primitive mesenchyme, and the form and structure of its cells and stroma conform to that of primitive mesenchyme. Some cells become compressed and assume a compact spindle shape adopting the appearance of a fibroblast with the neoplasm and simulating a fibrosarcoma. Stout believes that other cells of mesenchymal origin are not present within a myxoma, thus the presence of lipoblasts chondroblasts and others would not permit the diagnosis of myxoma. Myxomas have been produced experimentally in animals by the injection of certain viruses

DEGREE OF MALIGNANCY

Myxomas are believed not to metastasize. There have been a few reports of metastases from a myxoma of the heart, but since these were reported by one author (Fenster) Stout casts suspicion on the true nature of these neoplasms Inasmuch as they apparently do not metastasize, although they do grow both in an expansile manner and infiltrate contiguous structures Stout believes they should be labeled *myxomas* He does not accept the term *myxosarcoma* because of both pathologic criteria and the absence of metastasis. Myxomas infiltrate extensively and kill by invading

vital contiguous organs Myxomas in children are more malignant than those in the adult

INCIDENCE

Stout found over 100 instances of myxomas (exclusive of those of the heart) reported in the literature and has collected 49 additional cases from his laboratory

SEX AND AGE OF PATIENTS

Of the 46 patients reported by Stout, 25 were female and 21 were male Six of these patients were Negroes The tumor may occur in any age bracket In the group of 99 patients referred to by Stout, they were most frequent in the decade between 40 and 49 years, at which time 25 cases occurred The incidence gradually sloped off on either side of this peak age bracket There were 10 between the ages of 30 and 39, 11 between 20 and 29, 11 between 10 and 19, and 17 between 0 and 9 years On the side of the slope with increase of age, he observed 11 between the ages of 50 and 59, 13 between 60 and 69, and 1 in a patient aged 70 years Thus, there was nothing characteristic about the age groups It would seem that the myxomas of children tend to be located somewhat more frequently in the genitourinary system, involving the bladder, spermatic cord, and other structures of these systems The myxoma histologically is not unlike the sarcoma botryoides seen in little girls, and they are no doubt related oncologically. (See p 316 for discussion of sarcoma botryoides)

LOCATION

Of the myxomas recorded from the literature, exclusive of those of the heart, the distribution has been as follows in the subcutaneous and aponeurotic regions, 32, bones, 36, genitourinary tract, 23, and the skin, 22 They were located as follows in the other regions: retroperitoneum, 5, intestines, 5, nose and sinuses, 5, muscle, 4, joint, 4, pharynx and tonsil, 3, breast, 3, orbit and eyelids, 4, and 1 each in the cranium, spleen, appendix, liver, parotid gland, carotid body, and ear In the authors' series there were 3 patients bearing myxomas present within the retroperitoneal region In fact, the largest myxomas occur in this region, and Stout records one removed from a 36-year-old female which weighed about 5½ kg

CLINICAL COURSE

There is nothing particularly characteristic of myxomas except that in certain instances the myxomatous jellylike consistence is pathognomic. Sometimes this myxomatous quality is camouflaged as a result of pressure from contiguous organs or is completely hidden when it occurs in such dense regions as bone

Myxomas vary in size from small subcutaneous tumors to larger sizes, as in the organs of the genitourinary system or retroperitoneal region where they may grow unhampered by adjacent compressing tissues The largest myxoma recorded by Stout measured 30 × 10 cm and represented a recurrence after a previous excision Another, described by Leischner in 1930, was reputed to weigh 82 kg and measure 62 × 63 cm, it was attached to the labia majora, extending between the vagina and rectum Stout believes this was a liposarcoma.

The tumors tend to grow slowly and infiltrate deeply The duration of symptoms can vary from a few weeks to many years In Stout's series of 19 myxomas, the average duration of symptoms was four years The tumor may remain quiescent and grow very slowly for a long period, after which there may be evidence of increased activity attested

by rapid growth. The opposite course may ensue, and the tumor may grow very *rapidly at the onset and then seem* to run out of momentum and remain as a fixed or very slowly growing mass

The clinical appearance of myxomas in different sites presents more or less distinct characteristics. Those occurring in the skin or subcutaneously tend to produce a pressure atrophy of the skin which results in a glistening, shiny appearance of the overlying skin. These tumors tend to remain small. Those of the intestine tend to be pedunculated and produce the clinical symptoms resulting from intussusception. Myxomas of the genitourinary tract have been reported essentially in infants and children although they may occur in adults Myxomas have been described in the spermatic cord, and in view of the ontogenetic development of the organ, it is not surprising to find a tumor of primitive mesenchyme originating here.

Myxomas of the orbit and eyelid and myxomas of the mammary gland, as well as those of the upper respiratory passage, do not lend themselves to detailed discussion. For the most part they represent isolated reports and are oncologic curiosities. There is nothing specific concerning their natural history Those tumors described as myxomas of the larynx are probably laryngeal polyps in which there is either marked edema or myxomatous degeneration of a laryngeal polyp Those described as myxomas of the nasopharynx are essentially the nasopharyngeal angiofibromas described on p 212.

DIFFERENTIAL DIAGNOSIS

Two important lesions which must be distinguished from myxomas are (1) *ganglion* a secretory cystic tumefaction of tendon sheaths These lesions are cystic whereas myxomas are practically always of a semisoft or solid consistency (2) Localized *myxedema* while not neoplastic, presents a histologic picture of myxoma because it consists of a large quantity of mucinous ground substance in which are scattered, stellate cells and fine argyrophilic reticulin network.

TREATMENT

The treatment of this tumor is exclusively by wide surgical resection. Irradiation may be utilized for palliation, but its use has been uniformly unsuccessful. Tomanek reported a patient with a myxoma of the spleen which was made to shrink markedly after irradiation. Jacox and Freedman reported cures by irradiation of several myxomas of the finger These tumors could have been effectively treated also by surgical resection.

The biggest difficulty in treating these neoplasms by surgical excision is the lack of definite boundaries which outline the true extent of the tumor. Pseudopodia of the tumor infiltrating contiguous structures are common, and unless the surgical resection is adequate, recurrences will be the rule. There have been several reports of repeated recurrences which attest to the tendency of this tumor to remain localized, as well as to the inadequacy of the surgical resection. Hand and O Connor report a patient with a myxoma of the external ear which required several excisions due to repeated recurrences The result was total loss of the ear Trabucco described a myxoma which recurred at least eight times following surgical excision during the long period of 35 years.

The method of planning the proper therapeutic approach for this particular neoplasm depends exclusively upon an exact histologic diagnosis *Frequently* these tumors are small and appear clinically innocuous. The tendency is to be conservative in the resection. Study of a frozen section is frequently not suitable to establish the exact diagnosis in this particular group because of the varied

histologic appearance in different portions of the neoplasm Thus, one portion may consist exclusively of myxomatous ground substance and a diagnosis of ganglion may be suspected, whereas other regions may consist of compact spindle cells presenting an appearance of a fibroma or fibrosarcoma It is accordingly considered wise to excise the tumor in toto If, following analysis of paraffin sections, the diagnosis of myxoma is established, then a wider resection is performed In certain instances one may take advantage of the failure of this tumor to metastasize and remain conservative even after the diagnosis of myxoma has been established This may be indicated for certain myxomas in exposed regions, especially those of the finger tips or the soft somatic tissues, which lend themselves well to clinical detection In such instances, careful follow-up is indicated, and at the first sign or the first suspicion of a recurrence, a wide local resection is performed

PROGNOSIS

In Stout's series of 27 patients who were followed for a suitable period, 5 were alive without evidence of tumor 5 years and longer, and 9 were alive without evidence of tumor for less than 5 years Stout recorded 3 patients who had been alive with tumor for over 5 years One of these had a myxoma of the mandible of 9 years' duration, 1 had a myxoma of the leg of 16 years' duration, and the other a myxoma of the neck of 30 years' duration The fact that these patients had lived for such prolonged periods and still presented evidence of the presence of myxoma indicates the benign clinical course which some of these tumors may assume

Stout listed 7 patients who were alive with evidence of tumor for less than 5 years Three have died, 1 following an operation for the myxoma, 1 as the result of the tumor, and 1 from an intercurrent disease with the tumor persisting

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MESENCHYMOMA*

DEFINITION

Mesenchymomas are rare tumors which derive from the primitive mesenchyme Unlike the myxoma, which retains the form and structure of the primitive mesenchyme mesenchymomas develop along the pathways of normal maturation of mesenchyme and thus the neoplasm will manifest two or more mesodermal cell types

The primitive mesenchymal cell is endowed with amazing growth energies and is the ultimate ancestor of the various tumors of the soft somatic tissues, both benign and malignant. In the ordinary course of differentiation these mesenchymal cells finally emerge into specific functional tissues, such as fat, muscle, fascia, nerve, synovium, etc. but seldom in pure form because of the variable proportions of stromal elements which are present. The connective or fibrous tissue component of the somatic tumors may constitute a relatively small proportion of the neoplasm as in some liposarcomas, or a major part of the bulk as in some malignant synoviomas The preponderance of connective tissue in some sarcomas has led to the erroneous appellation *fibrosarcoma* without due consideration of the histogenesis of the more differentiated type of cell which is present but less conspicuous The term *mesenchymoma* as employed by Stout excludes from the classification any tumor in which one of the two elements is fibroblastic, and rightly so because fibroblasts are always elaborated by synovial cells in synovial sarcomas as well as in most other sarcomas. Also excluded are tissues of metaplastic change such as the occurrence of bone in liposarcoma or the development of sarcoma in myositis ossificans

GENESIS

The mixed mesenchymal tumors are comprised of two or more somatic tissues of different histogenesis in addition to the variable proportions of fibrous stroma present Theoretically *the mesenchymomas should be frequent instead of rare* The neoplasm may contain adipose, angiomatous, osseous, cartilaginous hematopoietic, myxomatous and smooth muscle tissues, but such multiple admixtures are seldom found. Each of the component tissues may be as fully malignant as any sarcoma of pure histogenetic type. The potpourri of tissues varies widely in composition and in degree of malignancy In lieu of the term

* In collaboration with James R. Lisa.

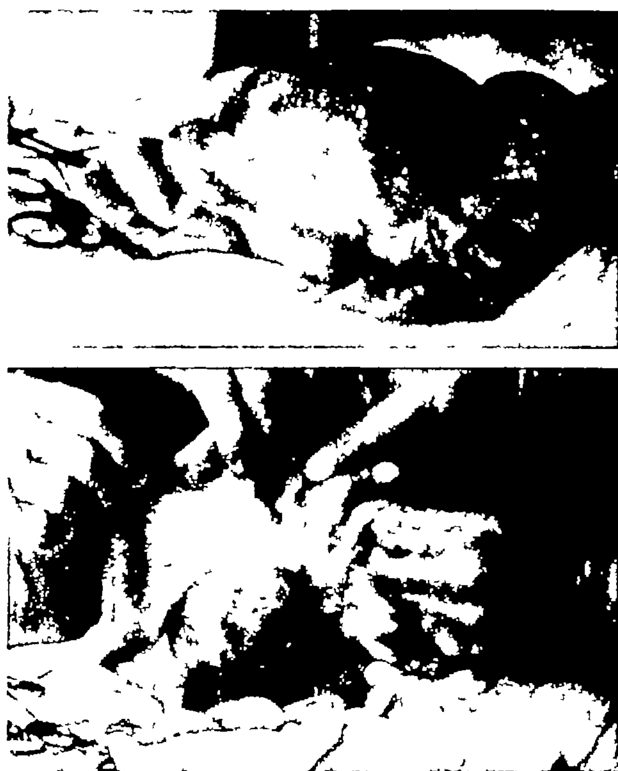


FIG 160 A mesenchymoma in the mesentery of the ileum, photograph taken at operation (*Courtesy*, Hyde, White, and Stout Cancer 3 353, 1950)

mesenchymoma, implying a malignant tumor, compound terms have found some usage in medical literature, but Stout's identification of them in the single category is a definite titling which should be adopted Some of the sarcomatous elements are in greater proportion than others, therefore, there is no set pattern of composition

Although Stout admits that metaplasia may play a role in the genesis of these tumors, he is inclined to consider them largely as dysontogenetic neoplasms, originating as developmental aberrations An argument in favor of metaplasia, he points out, is the possible occurrence of heterotopic bone and cartilage, whereas in substantiation of the dysontogenetic theory is the occurrence of mesenchymomas in regions wherein congenital abnormalities are found The presence of neoplastic cells of epithelial origin vitiates the diagnosis of mesenchymoma When present, the neoplasm would be classified into the carcinosarcoma category (see Chap 15), and if entodermal elements are present, the neoplasm would be teratoma

The absolute diagnosis of the mesenchymoma by purely histogenetic criteria can be difficult in view of the wide variety of tumors which contain admixtures of several cell types Thus fibrolipomas of the skin will contain two elements of mesodermal origin, and lipomas of the kidney may contain evidence of hematopoiesis

INCIDENCE

Mesenchymomas are extremely rare and for the most part have been reported in the literature as isolated cases The neoplasms reported by Amolsch which contained chondroblasts, rhabdomyoblasts, and myxomatous tissue and occurred as polypoid growths in the vagina and uterus are probably examples of mesenchymoma The case reported by Dreyfuss and Lubash, a tumor of the spermatic cord of 14 years' duration, was composed of both osteogenic and liposarcomatous elements One reported by Desaive and Closon, a fibrolipomyxoma of the diaphragm, also most likely represents an example of a mesenchymoma.

Stout recorded eight instances of mesenchymomas, seven of which were malignant They occurred as follows one in the gluteal muscle, one in the rectus femoris muscle, one in the posterior thigh muscle, one in the uterus, another in the lateral portion of the neck, one developed from the pleura, and one from the subcutaneous region of the leg, and an additional one arose from the liver He also recorded an interesting instance of a mesenchymoma, apparently benign, arising from the mesentery in a 36-year-old Negro woman (Fig 160) This tumor was made up essentially of mesodermal elements which were essentially benign They consisted of blood vessels and smooth muscle, portions of which were myxomatous Although histologically this tumor was benign, Stout calls attention to the fact that the apparently be

nign mesenchymomas have a propensity to recurrence and thus may be potentially clinically malignant.

Most mesenchymomas reported have been malignant neoplasms with tremendous potentiality to infiltrate and invade all contiguous structures and occasionally to metastasize. There are not enough data to comment upon age, sex or other clinical hallmarks of this tumor Those reported in the literature to date, however have demonstrated a natural history which is essentially that of a malignant neoplasm with great infiltrative ability

TREATMENT

The only treatment for this neoplasm is the most radical surgical extirpation with ruthless sacrifice of the containing tissues viscus, or extremity The radical surgical extirpation must be performed early in the course of this neoplasm because, since it is a nonencapsulated infiltrating growth, the tumor develops linear strands which course through fascial planes or invade whole segments of contiguous structures, so that the development of planes of resection becomes difficult, if not impossible, during the later stages.

Radiation therapy has little, if any ability to arrest this neoplasm It may be administered for palliative purposes in those patients in whom the tumor is found inoperable. The following case report demonstrates the natural history of a mesenchymoma treated by the authors and indicates the ruthlessness by which this neoplasm can expand and compromise all contiguous tissues.

CASE REPORT NO 14

C K a 54 year-old white male, was first seen on October 14 1949 In May 1949 he had observed in the left upper anterolateral abdominal wall a lump which was resected elsewhere shortly thereafter At that time a portion of both the ninth and tenth ribs was removed. Within two months a recurrence had developed in the medial aspect of the incision involving the abdominal wall X ray therapy had been given without apparent effect. His weight was maintained at 208 lbs

At the time of our first examination a fungating recurrent sarcoma was seen to involve the left lower anterolateral chest wall, adherent to and involving the ribs. It was fixed and immovable, and no palpable lymph nodes were discovered. A roentgenogram of his chest revealed evidences of pulmonary metastases in the lower portion of the right lung field in the posterior gutter The diaphragm moved well, ventilatory excursion was adequate, and the patient had good respiratory reserve

The patient refused surgical intervention and went to a tumor hospital in Philadelphia. While there he received fractionated treatments with polysaccharides at monthly intervals, starting on November 31 1949 and continuing until April 16 1951 During this time the recurrent tumor of the chest wall tripled in size when he returned in May 1951 the huge fungating tumor was as shown in Figure 161 In the meantime he had lost considerable weight. The roentgenograms of the chest now showed the pulmonary metastases to be much larger

Operative Treatment

On June 11 an operation was done by making an incision along the course of the twelfth rib with extension inferiorly and medially toward the midportion of the abdominal wall. The skin was then dissected away from the mass and by encompassing the contours of the tumor the musculature of the abdominal wall which had become extremely frayed, was dissected away from the mass. The external oblique, transversalis, internal oblique and left rectus muscles were transected, and in one portion of the abdominal wall, where the tumor had infiltrated these muscles and the peritoneum it was necessary to excise all of these structures leaving a huge defect in the abdominal wall As the dissection progressed

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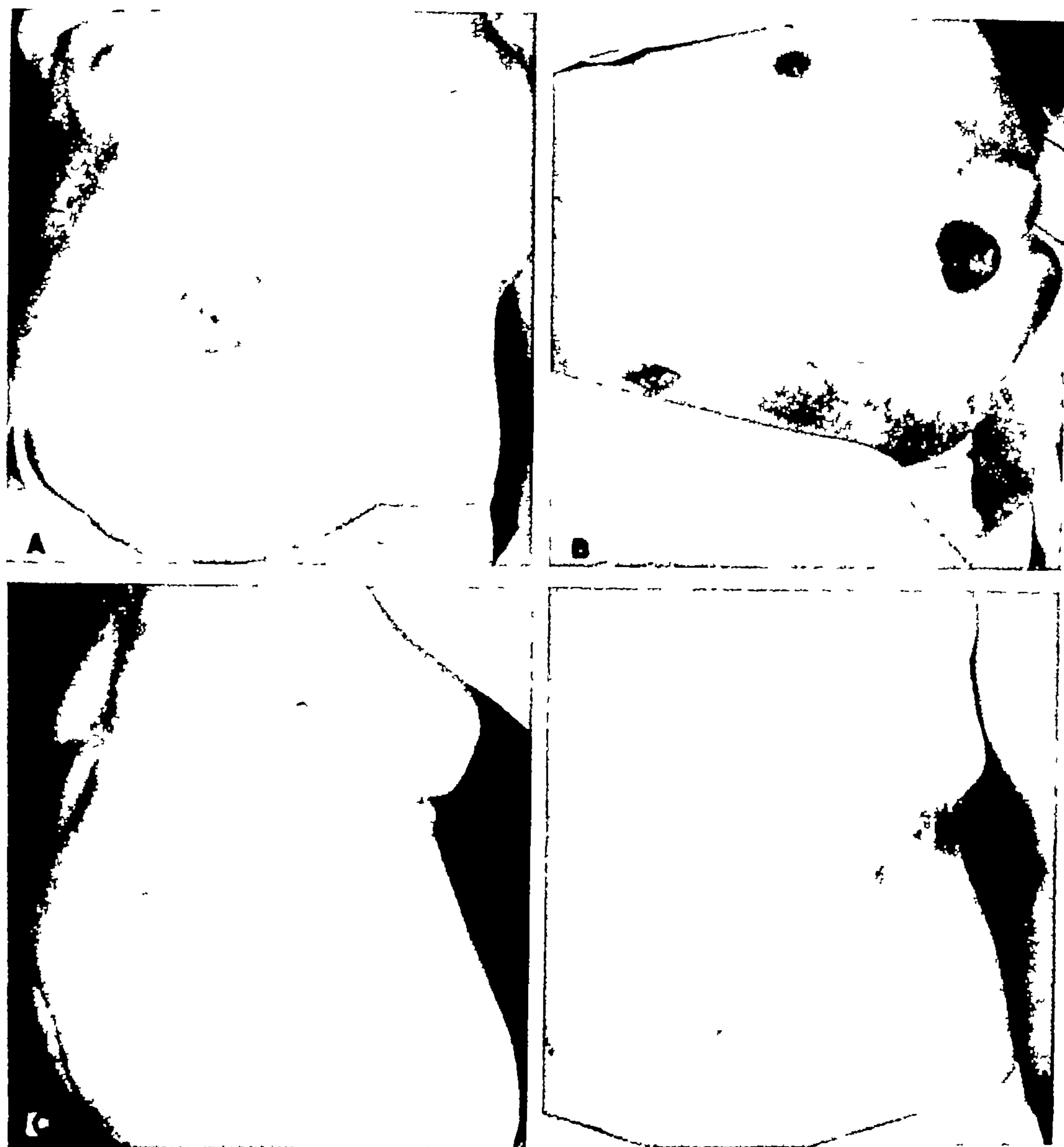


FIG 161 *A* Clinical photograph of a mesenchymoma, anterior view Note nodularity and bulk of tumor It involves both abdominal and thoracic walls *B* Another view to illustrate lateral protuberance *C* Anterior and lateral views of the patient postoperatively after removal of a large segment of abdominal wall, costal margins, and portions of diaphragm and pericardium The defect was closed by tantalum mesh under the skin (Pack and Lisa, Surgery 35 277, 1954)

superiorly, it was necessary to resect the lower three ribs, after which the intrathoracic portion of the mass was excised by removing a portion of the pericardium and a large segment of the left leaf of the diaphragm Numerous implants of the tumor were noted within the substance of the lung, on the diaphragm, and on the parietal pleura

After the huge tumor mass had been dissected free from the body wall and removed, the resultant defect was repaired by suturing the diaphragm to the chest wall at the level of the ninth rib The chest wall was then closed with interrupted silk sutures, and a drain was placed under water The abdominal cavity was closed by suturing the peritoneum and the remaining abdominal musculature in the four quadrants of the defect to each other, leaving a central defect 10 × 10 cm, which was repaired by suturing a tantalum mesh in place, over which the skin was approximated The tantalum mesh was in direct contact with the viscera and was the only structure intervening between the subcutaneous fat and the viscera

Postoperative Course

Convalescence was completely uneventful The wound healed well The patient gained 20 lbs after the operation The



FIG. 162. Mesenchymoma, showing the external nodular appearance of the skin (*top*) the nodular appearance of the undersurface (*middle*) and the cut surface (*bottom*) (Pack and Liu, Surgery 35 277 1954.)

metastases in the lungs remained relatively quiescent. Six months later pleural effusion developed, requiring thoracentesis. He died ten months after the date of operation The period of complete palliative relief was approximately six months

Gross Pathologic Anatomy

The tumor was a huge, grossly nodular mass measuring 34 0 × 23.5 × 11 8 cm and was covered by a triangular segment of skin with a healed central surgical scar The mass was divided into lobules of milky white or yellow white firm tissue with occasional hemorrhagic foci It was tightly adherent to the periosteum of the rib segments (Fig 162)

Histologic Features of the Tumor

The neoplasm was extremely vascular Within the tumor could be seen thin-walled blood vessels lined by neoplastic endothelial cells lying in a relatively loose tissue with necrobiotic foci (Fig 163 *upper left*) Other portions were much richer in blood vessels and lay in tissue which had the same type of cell as that which lined the vessels Other segments of the neoplasm (Fig 163 *lower left*) were more cellular some foci resembled primitive cartilage.

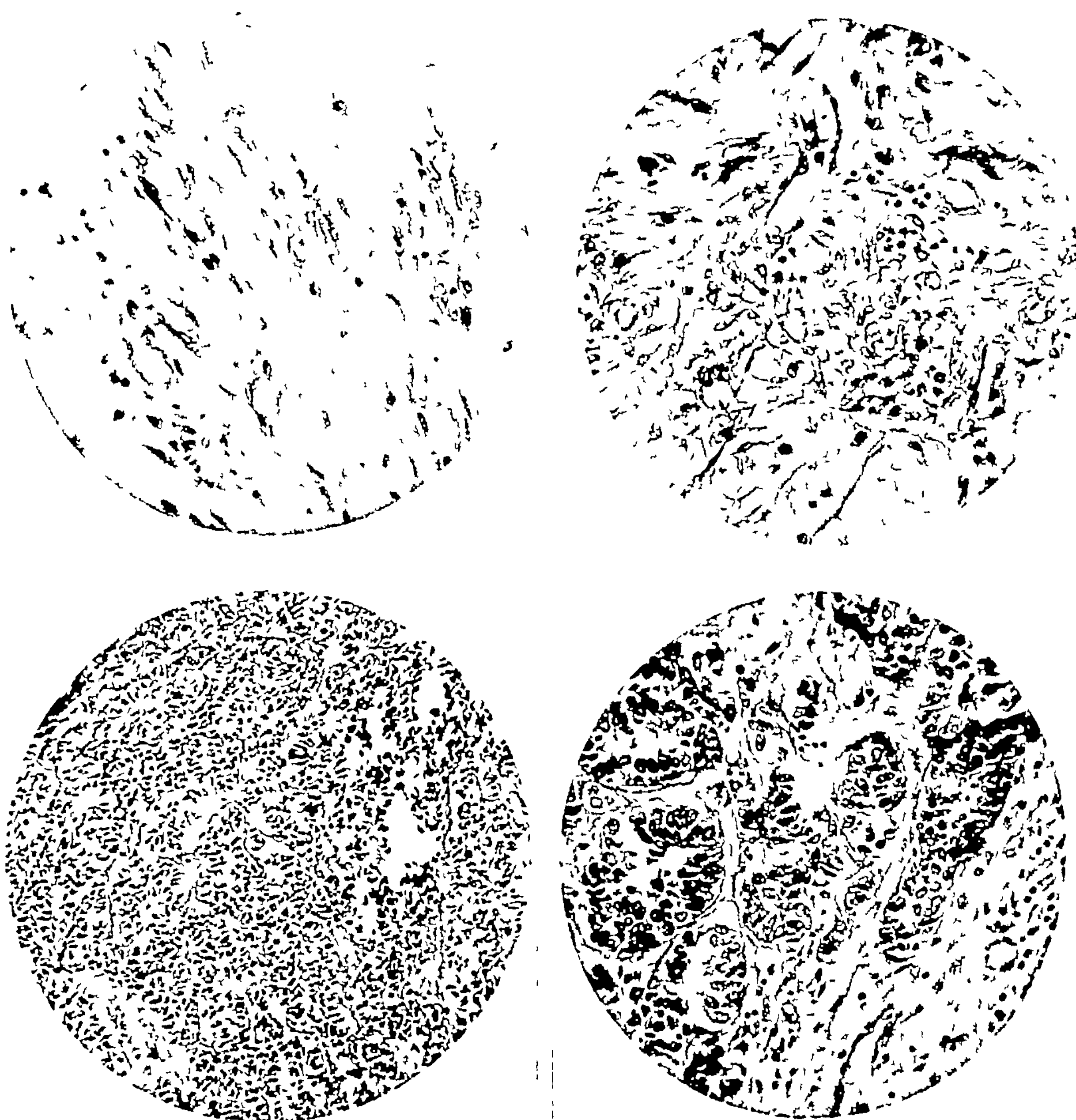


FIG 163 Mesenchymoma (*Upper left*) The vascular channels are lined by endothelial cells showing moderate anisocytosis and hyperchromia They merge into the surrounding tissue, which has a few cells of similar nature. There are foci of necrobiosis (× 200.) (*Upper right*) Vascularity is more marked. The endothelial cells display a greater degree of anisocytosis, and the surrounding tissue is richer in neoplastic elements (× 300) (*Bottom left*) The richly cellular area closely simulates epithelial structures Other foci reveal primitive chondroblasts (× 70.) (*Bottom right*) The neoplastic cells arise directly from the wall and produce solid nests filling the channels There is marked anisocytosis and hyperchromia Mitoses are present in moderate numbers There are a few inflammatory cells (× 300) (Pack and Lisa, Surgery 35 277, 1954)

These channels were lined by malignant cells similar in character to those of the other areas but displaying more anaplasia and anisocytosis A moderate infiltration by inflammatory cells was present

Pathologic Diagnosis

Mesenchymoma of the thoracoabdominal wall.

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CHAPTER 17

Osteoblastic and Chondroblastic Tumors of the Soft Somatic Tissues

THE ossification and chondrification of lesions within soft tissues outside the skeleton occurs frequently The well-known calcification with resultant ossification, in sites of physical trauma or within hematomas, has occurred in rather great numbers The formation of localized myositis ossificans following repeated irritation to the soft somatic tissues, as occurs in those individuals who, for example, frequently ride horseback and develop this syndrome involving the great muscles of the thigh, is a well-known entity Evidence of the existence of extraskeletal ossification as a result of metabolic derangements is exemplified by the entity myositis ossificans progressiva (described on p 202) Calcification and ossification are those manifestations of degenerative metabolic alterations which occur so uniformly in arteriosclerosis Such changes occur also in chronic granulomatous lesions, as tuberculous granulomas, etc

Examples of chondroblastic and osteoblastic tumors occurring extraskeletally have been repeatedly recorded Instances of ossification of intracranial neoplasms not connected with the skull have been described by Alpers, who calls attention to an osteochondroma arising from the dura and cites intracranial chondromas arising from the dura Magnien and Perrot (1933) described an osteoma of the tongue and Parsons and Henthorne (1944) reported an osteogenic tumor of the lip Osteogenic sarcomas are reported to have arisen from the bladder, and the opinion has been expressed that they arise from mesodermal derivatives of the wolffian body Chondromatous tumors occur within the breast rather frequently in certain species of dogs but the counterpart in human breasts is much less frequent Boneti in 1700 reported an osteoma of the breast in a woman and since then a number of such incidents have been observed Ross in 1937 cited 8 instances of osteogenic sarcoma of the breast

These tumors may occur anywhere in the body They can occur in parenchymatous organs as well as within the soft supporting structure of the organism Thus, in the series of 30 cases gleaned from the literature and reported by Wilson there were 12 bonelike tumors occurring within the breast and 7 within the thyroid gland He also recorded 1 in the gallbladder and 1 in the kidney region Also, of the 15 instances which

he reported in his own series, there was 1 osteoma from the perirenal region Kretschmer also has reported a perirenal retroperitoneal osteosarcoma. This is not surprising, as the fat in this loca tion may adapt other bone functions and extramedullary hematopoiesis is noted in this site. These observations suggest that the fat of this region may be of a specialized form of adipose tis sue. Several chondromatous tumors aris ing from the parenchyma of the lung have been reported, and Greenspan cited an instance of an osteoid chondrosarcoma of the lung

Those osteoblastic and chondroblastic tumors which have arisen from the soft somatic tissues have occurred in various locations The most frequent site was the lower extremity the upper extremity was next in frequency and instances have been described of osteogenic sarcomas occurring within the abdominal wall, retroperitoneal parietes the soft tissues of the chest, neck, and other sites Ex amples have been reported of tumors which were either pure osteomas osteosarcomas, chondromas chondrosarcomas or a combination of osteo- and chondromatous structures

INCIDENCE OF EXTRASKELETAL OSSIFYING TUMORS

These tumors are not common Wilson was able to find 30 cases recorded in the literature to 1941, and he recorded 15 instances obtained from the Department of Surgery and Pathology of the Uni versity of Chicago and the registry of bone sarcoma of the American College of Surgeons Stout has recorded 13 in stances from the files of the laboratory of surgical pathology at Columbia Uni versity Seven of them were osteogenic sarcomas, of which 3 occurred in the lower extremity 2 in the upper extremity 1 on the trunk, and 1 in the perirenal region. Of the chondrosarcomas 4 occurred in the lower extremity and 2 in the upper extremity

ETIOLOGY OF EXTRASKELETAL OSTEOGENIC TUMORS

The reason why tumors containing characteristics of chondroblastic or osteogenic neoplasms occur in soft tissues remains an enigma. The different theories pertaining to the formation of myositis ossificans progressiva are presented in Chapter 15 The great versatil ity of cells of mesodermal origin in dif ferentiating along the various paths of mature structural tissues has been amply discussed, and it is possible that the chondrosarcomas and osteogenic sar comas occurring in the soft tissues reflect metaplastic histogenetic alterations of the fibroblasts or some other mesodermal cell. The theory of misplaced periosteum does not seem tenable It is possible that alteration in pH or other physical or chemical changes within a given region of tissues will be a deter minant in deciding the course of differ entiation of a cell in that region. It is thus possible that the etiologic agent, whatever it may be, produces the stim ulus for the neoplastic proliferation and that the alterations in the environs of the cell undergoing these changes determine the route of differentiation which the neoplasm will follow

Osteogenic sarcomas can be produced experimentally in the soft tissues of rats, as has been determined by Dunning, Curtis and Bullock who injected 1 2 benzpyrene subcutaneously into a group of rats two of whom developed osteogenic sarcomas. Brunschwig and Roome produced spindle-cell sarcomas in the suprarenal gland of rats by implanting crystals of methylcholanthrene into the organ, and within the spindle-cell sar coma were small foci of *ossification*. A recent report of an extraskeletal osteogenic sarcoma which arose in irradiated tissue, *irradiation* having been given as

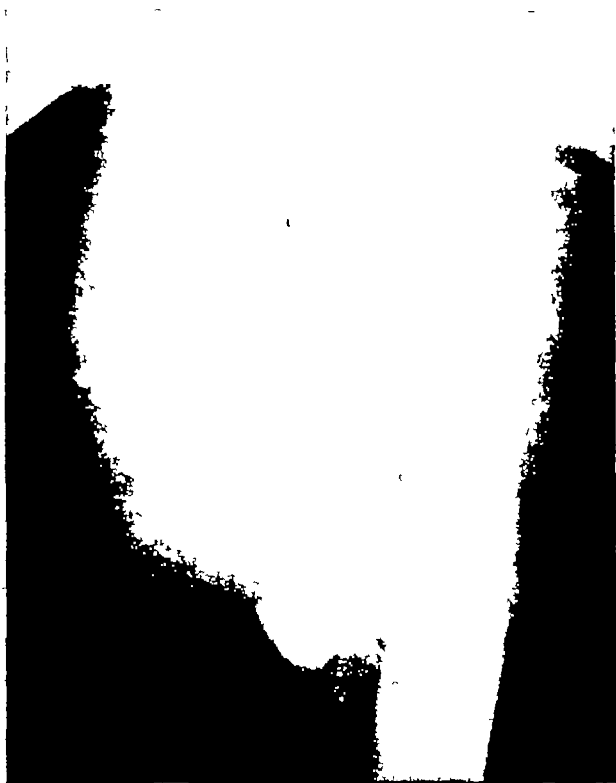


FIG 164 Development of osteogenic sarcoma in myositis ossificans Roentgenogram showing calcification in muscle Extraosseous osteogenic sarcoma developed in this mass.

prophylactic therapy for a teratoma, demonstrates that irradiation may be an etiologic factor in producing extraskeletal ossifying sarcomas just as it may be a factor in producing osteogenic sarcomas of bone, as has been demonstrated on repeated occasions

Leriche and Policard believe, as originally suggested by Virchow, that osteogenic sarcomas of the soft tissues are essentially fibrosarcomas which have become passively ossified as a result of environmental situations Mallory also accepts this explanation and calls attention to the fact that many of the bony tumors which arise in the soft somatic tissue are not truly neoplasms but represent metabolic alterations within the ground substance

Binkley and Stewart propose the rather unique theory that the heterotopic bone changes are related to the blood vessels, the onset of the neoplasm being a capillary angioma in which fibroblasts are interspersed The capillary walls undergo changes with subsequent obliteration of the capillary which produces hyalinization with resultant calcification and ossification. They believe that these tumors are essentially of connective-tissue-cell origin, with the alteration occurring in the extracellular substance as a result of environmental alterations

Stout questions whether these neoplasms are pure tumors or whether they represent tumors which consisted originally of various cell components—essentially a malignant mesenchymoma With continued development of the tumor the other cell types disappeared by means of attrition, the result of overgrowth of the osteoblastic and chondroblastic components, so that the end result is an apparent osteogenic sarcoma or chondrosarcoma Stout calls attention to the fact that this sometimes happens in teratomas and speculates on this modus operandi for the formation of extraskeletal osteogenic sarcomas and chondrosarcomas, and promulgates the belief that they may actually represent malignant mesenchymomas Further investigation is necessary for understanding the nature of osteogenic and chondroblastic sarcomas of soft somatic tissue

The origin of osteogenic sarcomas in myositis ossificans has been described by Pack and Braund They have reported three patients with myositis ossificans who presented clinical and histologic criteria of malignant neoplastic changes within foci of the myositis ossificans lesions, with the development of metastases and even death, the result of the sarcomatous transformation

Another similar occurrence of a soft somatic tissue osteogenic sarcoma has since been observed in a 38-year-old female who had a rapidly growing grapefruit-sized mass involving the abductor muscle of the right thigh. The mass was excised but soon recurred Roentgenograms revealed a calcific mass (Fig 164) in which the malignant trans-



FIG. 165 Low power photomicrograph showing the neoplastic appearance of a section of the tumor shown in Fig. 164.

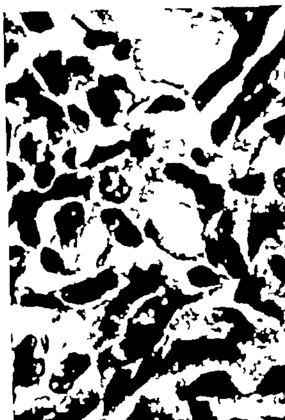


FIG. 166. High-power photomicrograp Fig. 165 demonstrating that the neoplasm osteogenic sarcoma.

formation occurred (Figs 165 166) She died from pulmonary metastases 9 months after the clinical manifestation of the tumefaction

A number of authors have questioned the reliability of diagnosing osteogenic sarcomas within myositis ossificans because the histologic appearance of myositis ossificans will present, in addition to normal appearing bone sections grotesque osteoblasts in an undifferentiated form which have many of the characteristics of an osteogenic sarcoma

The clinical course of the patients reported by Pack and Braund, with the development of distant metastases and the extremely rapid growth of the neoplasm, leaves no doubt regarding the diagnosis of sarcoma. Such studies indicate that the natural history of the disease as manifested by the clinical behavior of the patient may sometimes be a more reliable criterion for establishing a diagnosis in certain of these borderline situations than is even the histologic appearance of the lesion. About six instances of sarcoma developing in le of myositis ossificans have been corded. The course of the patients form the report presented by Pack Braund will be appended to this ch to demonstrate the nature of the comatous transformation of myositi sificans progressiva.

DEGREE OF MALIGNANCY OF SOF TISSUE OSTEOGENIC SARCOMAS

Rhoads and Blumgart have expr their belief that, although these plasms appear malignant histologi they are clinically benign. They reco 2 patients a male aged 37 with an c blastoma of the left groin of 15 mo duration and a 21 year-old female an osteoblastoma in the right thigh, had remained well 7 years an years, respectively after local exc Stout has remarked that osteogenic comas and chondrosarcomas of the tissues are often less malignant clin than their congeners in bones. He v

that they may become fully malignant and cause the death of the patient In this regard it is pertinent to call attention again to the report by Wilson of 30 instances of osteoblastic and chondroblastic tumors from the literature to 1941 Mention is made of the death of 4 patients from the sarcoma It is, however, impossible to arrive at any statistical mortality rate because follow-up study is mentioned so infrequently in his review Of the 15 of his own series, 4 were recorded as having died from the tumor, and the clinical description strongly suggests that death also occurred in 3 others In 1 there was no mention of follow-up observation, and in 2 the diagnosis was recorded as benign osteoma

Of 4 patients studied by the authors, in whom sarcoma formed on the basis of myositis ossificans, all have died as the result of the sarcoma

These data focus attention upon the malignant nature of chondrosarcoma and osteogenic sarcoma occurring in the soft somatic tissues They may behave as do those tumors arising within the bone, they may be fully malignant, produce metastases to the lungs and other organs by means of blood-stream embolization, and cause the death of the patient

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis one must distinguish between so-called parosteal sarcomas which arise from the joint capsule or from an exophytic periosteal extension or fascial attachment to bone They resemble chondromas but are not infrequently highly malignant and behave like osteogenic sarcomas of the skeleton

Giant-cell tumors of tendon sheaths which may have calcific or osseous components are believed to represent metaplasia of the synovial tissue This subject is discussed in Chapter 20

TREATMENT OF OSTEOGENIC AND CHONDROBLASTIC SARCOMA IN THE SOFT SOMATIC TISSUES

If one is assured of the diagnosis of osteogenic sarcoma in the soft somatic tissues, the treatment of choice is amputation. However, many of these tumors are less malignant than their counterparts arising in the skeletal system A more conservative surgical procedure may be utilized, such as a wide local resection of the neoplasm Apparent cures of three patients (two reported by Rhoads and Blumgart and one by Coley) with osteogenic sarcomas of the soft somatic tissues treated by local resections of the neoplasm attest to the rationale of conservative resection in certain instances The demise of four patients of our series, however, emphasizes the malignant nature of some of these neoplasms

CASE REPORT NO 15

A 36-year-old white male suffered a tumor in the right thigh The familial and past histories were irrelevant

Sixteen years previously, while running a cross country race, he injured the muscles of the upper part of his right thigh Following this injury (the so-called charley horse), a firm, painless mass developed in the muscles of the upper medial part of the thigh and remained inactive for 16 years Two months before admission the upper portion of the mass became larger and was aspirated by his family physician Approximately 4 oz (120 cc) of serosanguineous fluid was obtained Roentgenograms revealed a large, irregular, pedunculated, calcareous mass in the soft tissues of the medial aspect of the thigh, apparently attached to, but not a part of, the femur (Fig 167) The cortex of the femur was not invaded Three weeks before admission an attempt was made to remove the mass The tumor capsule was ruptured in removal The wound was swabbed with acetone

The physical findings on admission to the



FIG. 167 Roentgenogram showing a large ossified mass in the upper part of the right thigh. The lower portion had undergone malignant degeneration showing on histologic examination spindle-cell osteogenic sarcoma. (Case report No 15) (Pack and Braund, J.A.M.A. *119* 776 1942.)

hospital were essentially normal except for the local lesion. Over the upper inner aspect of the right thigh there was a recently healed wound 13 cm long, beneath which was an indefinitely outlined area of thickening of the soft part extending from Poupart's ligament downward about 20 cm A roentgenogram of the chest was negative for pulmonary metastasis The tumor was diagnosed on microscopic study as spindle-cell osteogenic sarcoma

Treatment

The tumor was treated with the 4 gm. radium-element pack, 120 000 mgh. being given at a 15 cm radium-skin distance after which interstitial radon was inserted for a total of 53 mc. destroyed. He was then given twenty sessions of high voltage roentgen therapy 200 r each, through a circular port 10 cm in diameter (factors 200 kv 0 5 mm copper filter 63 cm target-skin distance) Six months after admission roentgenograms of the chest showed pulmonary metastases. The patient become progressively worse and died thirteen months after the clinical onset of the rapid growth of the thigh tumor

CASE REPORT NO 16

A white man aged 27 was admitted because of a recurrent tumor of the right thigh (Fig 168) The familial and past histories were negative

Twenty-two months previously a tumor mass measuring 2 cm in diameter was removed from the right thigh in another institution Microscopic examination of the specimen was not made Seven months later a local recurrence of the tumor was noted The tumor was surgically excised at the same institution A course of high voltage roentgen therapy (factors unknown) and one course of Coley's toxins followed.



FIG. 168 Osteogenic sarcoma developing in myositis ossificans Upper thigh, showing visible tumor (Case report No 16) (Pack and Braund, J A M A *119* 776, 1942)



FIG 169 Sarcoma in myositis fibrosa progressiva (Meyenburg's disease) Reproduction of infrared photograph showing the bulging tumor mass over the right scapula and dorsum of the chest (Case report No 17) (Pack and Braund, J A M A *119* 776, 1942)

Eleven months later a second recurrence was noted in the original scar, and the patient received additional high-voltage roentgen therapy

Physical examination was normal except for the local tumefaction On the anterior surface of the right thigh, over the trigone, was a healed scar in the midportion of which was a firm, nodular, circumscribed tumor measuring 2 × 2 5 cm A second scar and nodular mass measuring 4 cm in diameter was found on the posterior medial surface of the thigh below the apex of the adductor canal The skin showed evidence of recent irradiation A roentgenogram of the chest showed a spherical opacity typical of metastasis in the center of the right lower lobe Examination of the femur and pelvis was negative for bone involvement The pathologic report on submitted slides from the specimen removed previously was of osteogenic sarcoma, presumably beginning in either a hematoma or myositis ossificans

Treatment

The patient was given twelve treatments of 200 r each through a 7 cm circular port over the tumor in the thigh (factors, 200 kv, 0 5 mm copper filter, 63 cm target–skin distance) The pulmonary metastases were treated palliatively by roentgen rays and the radium-element pack The patient died from cerebral metastases one year after admission Permission for autopsy was not obtained

CASE REPORT NO 17
MYOSITIS FIBROSA PROGRESSIVA, DEVELOPMENT OF SARCOMA

F M, a 7-year-old boy complained of a swelling involving his right shoulder Six weeks prior to the initial examination, the tumor was first noted and it gradually increased in size (Fig 169)

The patient was undernourished The shoulder showed slight limitation of motion There was microdactylia of both hands and feet, especially noticeable in the thumbs, fifth fingers, and first toes (Fig 99).

Muscular System

In the left posterior cervical region, a pencillike calcification was palpated Two calcified plaques were noted in the spinus muscles just to the left of the midline in the lower thoracic and upper lumbar



FIG. 170 Photomicrograph of neoplasm in Fig. 169 demonstrating all the pathologic features of the sarcoma which had developed in the muscle, the site for many years of *myositis fibrosa progressiva*.

regions. In these plaques the bone was freely movable in the prone position but became fixed with muscle contraction (Fig 98)

Local Tumor

A symmetrical firm tumor was noted overlying the right scapula. It extended medially between the scapula and the spine as an ill-defined, diffuse tumefaction infiltrating the right trapezius and rhomboid muscles It also extended up into the supraspinous fossa The scapula seemed to be pushed forward by the tumor X rays of the chest and shoulder showed no evidence of pulmonary metastasis or bone involvement. Irregular calcified plaques were noted along the right axillary line in the left cervical region, along the crest of the right scapula, along the upper border of the humerus, and in the paralumbar region on the left side. Additional skeletal roentgenograms showed an exostosis of the medial portion of the head of the right tibia and probable small osteomas with broad bases in the medial and upper portions of both tibial shafts There was anomalous epiphyseal development of the bases of the second and fifth metacarpal bones, and the digits showed bilateral microdactylia Both feet showed a similar deformity of the first digits

On August 2, 1940 a formal biopsy of the tumor was obtained It was reported as a malignant tumor probably sarcoma of undetermined histogenesis Postoperative irradiation was given through two portals, 17 × 17 and 15 × 18 cm. a total dose of 3000 r × 2 (factors, 250 kv 1.5 mm of copper filter 50 cm target–skin distance) In October a second course of irradiation giving 2800 r with the same radiation factors was administered and complete regression of the tumor followed.

Metabolic Studies

The patient was readmitted March 18 1941 for the purpose of having a section of the muscle involved by myositis fibrosa removed for microscopic study and determination of whether there was any disturbance in his calcium-phosphorus metabolism.



Fig. 171. Rapid growth of recurrent sarcoma 7 years after radiation treatment. Interscapulothoracic amputation was refused. (Same case as Figs. 169 and 170. See also Figs. 98 and 99, case report No. 17.)

On March 28, he was given 0.4 mc. of radioactive phosphorus (P^{32}) and the following day was placed on a known calcium and phosphorus intake.

One week later a section of the involved muscle in the lumbar region was surgically removed. It grossly simulated fairly normal bone. There was a definite periosteum covering the external surface, a well-organized cortical portion, and what appeared to be a marrow cavity. Microscopically it resembled dead bone in tendon or aponeurosis.

During the preoperative control all fecal and urine excretions were carefully assayed; from March 29 to April 14, 1941, this child took a diet containing approximately 1 gm. of calcium and from 1.3 to 1.6 gm. of phosphorus daily. He was in strongly positive calcium and phosphorus balance, excreting an average of 194 mg. of calcium and 370 mg. of phosphorus daily. The partition of calcium and phosphorus between the urine and the feces showed no gross abnormality, though the urinary calcium was low. The findings appeared to be consistent with the picture of a previously poorly nourished child recently put on a liberal diet rather than of a child with a generalized abnormality in calcium-phosphorus metabolism. In the mineralized specimen removed on April 5, 1941, the phosphatase was of the bone type and the activity was greater than in that of any normal-growing bone. The



Fig. 172. Gross specimen of an extraosseous osteogenic sarcoma in a 57-year-old male. A hemipelvectomy was necessary for its extirpation. The patient died 10 months later. (Pack and Ehrlich, Ann. Surg. *124*:1, 1946. *Courtesy* J. B. Lippincott Company.)

radiophosphorus uptake was also high Adjacent uninvolved muscle was normal in phosphatase and radioactive phosphorus The findings indicate that the pathologic mineralization was due to local changes in the affected areas

Subsequent Course

This patient remained free of any recurrence of the sarcoma from 1941 until 1948 but during that interval the myositis fibrosa *progressed extensively* so that his neck and back became rigid, and the pectoral muscles became involved, with limitation of motion particularly in the right shoulder In August, 1948 the patient reappeared after a disappearance of four years A recent, more rapid growth in the right scapular region had caused apprehension and the child, now 15 years of age appeared *for treatment* Aspiration biopsy revealed sarcoma A roentgenogram of the shoulder showed a marked increase in the size of the soft tissue mass which now contained widespread regions of amorphous bone formation with invasion and destruction of the right scapula. The roentgen picture was *characteristic of osteogenic sarcoma* There was no evidence of metastasis to the lungs The tumor was huge and interscapulothoracic amputation was advised. This was refused by the parents The patient died on April 9 1949 of generalization of the sarcoma

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CHAPTER 18

Tumors of Adipose Tissue

TUMORS arising from fat present protean clinical expressions, the result of the universal distribution of fat within the organism and the fact that the tumors of fat can and do arise in practically any organ within the body. The majority of tumors arising from the adipose tissues are fortunately benign (21 cases of liposarcoma among 1,454 patients with lipomas reported by Stout and 12 liposarcomas among 490 tumors of fat reported by Geschickter) at the Memorial Hospital the ratio is 120 benign to 1 malignant tumor of fat. In addition to discrete lipomatous tumors are various entities either of neoplastic or metabolic origin which add to the diverse clinical manifestations of this entity. It is sometimes difficult to distinguish whether localized accumulations of fat are actually neoplastic or metabolic in origin. In most instances, histologic criteria may prevail to aid in this distinction. In other instances, the presence of a capsule will strongly suggest a neoplastic growth. However localized accumulations of fat without a capsule occur which infiltrate surrounding structures and are undoubtedly neoplastic. On microscopic examination only pure fat is observed. In other instances a capsule may have been ruptured, and the semidiffuse accumulation of fat may appear to be a metabolic derangement rather than a neoplasm. Because of this difficulty the nodular accumulations of fat will be considered under the general term *lipoma*.

Certain fatty accumulations, the result of metabolic derangements such as the adipose genital syndrome of Froelich caused by pituitary or adrenal disturbances, exophthalmos, the result of abnormal accumulation of fat within the orbit secondary to thyroid disturbances etc., will not be discussed in this chapter. The various entities of the so-called lipid dystrophies will not be elaborated upon.

LIPOMA

Lipoma is one of the most frequent benign tumors which afflict the human organism. A lipoma may occur anywhere within the body, and its gross characteristics are frequently dependent upon the site of origin. At the Memorial Hospital lipomas constituted only 4.3 per cent of all benign tumors. This low value is undoubtedly the result of the type of patient referred to that institution. Most

innocuous lipomas, especially those occurring subcutaneously, are excised by the local physician and not referred to a cancer hospital

Adair, Pack, and Farrior in 1932 presented a detailed review of 352 lipomas in 134 patients Although the majority of them are of congenital origin, most (40 per cent) make their recognizable appearance during the decennium 40 to 50 years, the age at which fat usually begins to accumulate The average age of the 134 patients was 43 years About 10 per cent of the lipomas occurred in children and were of rather bizarre formation

Lipomas are observed most frequently in females, 78 per cent of the patients observed by the Memorial Hospital group were females This sexual distribution is probably explained by the greater tendency of adipose tissue to accumulate in females and by feminine vanity which impels some women to seek treatment of their subcutaneous nodules They occur in all races They vary in size from tiny nodules to huge masses weighing more than the patient

ETIOLOGY

There is no known cause for the formation of lipomas Ewing has listed the following factors

1 A hereditary factor (as evidenced by the multiple symmetrical lipomas discussed later in this chapter)
2 Lipomas form in atrophying organs such as kidneys and breast (Virchow) or lymph nodes (Askanazy)
3 Multiple lipomas form in cases of, or following disease of the thyroid gland and other disease. Ewing believes that the regional overgrowth of fat in these situations is related to lipomas in the same manner that diffuse fibromatosis holds to fibromas (see p 352)
4 A congenital predisposition toward disturbances in the development of fat, including lipomatous overgrowth within such epithelial tissue as the brain.

He presents the following classification of fat overgrowth based on etiologic factors

1 Obesity
2 Localized overgrowth of fat tissue
3 Replacement lipomatosis, as in atrophic organs, bone marrow, kidney, and lymph nodes
4 Homologous lipomas (solitary lipomas, etc)
5 Heterologous lipomas arising from misplaced embryonal cells
6 Overgrowth of fat components in certain mixed tumors, as teratomas

An interesting feature of lipomas, as emphasized by Wells, is the fact that the fatty tissue of lipomas is not available to the body, even during starvation Patients with severe emaciation subsequent to catabolism of body fat and even essential protein, but with large quantities of fat captured within lipomas, have been observed

PATHOLOGY

Gross Appearance

The gross appearance of lipomas is essentially that of encapsulated fat The fatty mass is yellow and semifirm and is divided into smaller lobulations by fibrous strands which traverse the tumor. The tumor is almost uniformly encapsulated by a thin fibrous capsule which permits, as a rule, simple enucleation of this tumefaction from its tumor bed Cut section reveals the *homogeneous* yellowish, semifirm structure traversed by larger or smaller fibrous strands extending through the tumor in all directions The actual consistency of the tumor depends essentially upon the quantity of fibrous tissue within the

lipoma. In most instances there is a small quantity of fibrous tissue, giving a semifirm, unctuous characteristic. In other neoplasms a greater quantity of fibrous tissue exists and the mass will be of a firmer consistency There may be small cystic cavities within the tumor the result of liquefaction of fat. Smaller or larger *foci of hemorrhage* may be observed usually the result of trauma to the tumor

Histologic Characteristics

Histologically the tumor consists of typical fat cells. However many variations are observed. In certain tumors *only the typical adult cell may be present*. In others there may be an admixture of smaller cells All variations exist, from the adult plump fat cell, containing a clear cytoplasm which stains characteristically with special stains, to smaller polyhedral cells of embryonic types Occasionally the cells may contain granular lipoid pigments and thereby resemble xanthoma cells The presence of these cells has resulted in a rather complex terminology in which the tumors are termed *xanthoma lipomas* etc. Ewing called attention to certain lipomas in which there is an abundance of arterioles He labeled these vascular fatty tumors *lipoma telangiectatium* or *cavernosum* Lymph vessels are sometimes also rather common.

The exact cells of origin of lipomas are not known. It is believed that although these tumors exhibit all the characteristics of adult fat they do not arise from adult fat but rather from the mesenchymal primordial cell of fatty tissue. All variations may be observed, from the young, immature spindlelike cell of the prodromal cell through the various, *evolutionary* cytologic changes to the well-differentiated adult fat Careful search of a lipoma will sometimes reveal small foci of immature cell elements, which feature has led certain pathologists to diagnose these lipomas as being either potentially malignant or fully malignant. The presence of myxomatous tissue containing the spindle or stellate lipoblasts is regarded by Stout as fulfilling criteria of malignancy, in that they grow by infiltration and can be cured only by radical local resection He considered them as differentiated liposarcomas although they do not metastasize.

CLASSIFICATION

One may classify lipomas according to histologic or clinical criteria. Geschickter has classified them as (1) benign lipoma, (2) fibrolipoma or embryonic lipoma, and (3) liposarcoma In addition one may mention hibernoma, the tumor containing foam cells, which arises from the brown fat, believed by some to be the vestige of the hibernating gland. (This is discussed later in this chapter)

A workable clinical classification of lipomas consists of the following

I The simple solitary lipoma
II Multiple lipomas
III Congenital, diffuse lipomatosis
IV Degenerative lipoma.

I THE SIMPLE SOLITARY LIPOMA

The simple solitary lipoma the most frequent form of fatty tissue tumor occurs (1) subcutaneously (the most frequent site) (2) intermuscularly (3) in the intrathoracic or intraperitoneal (retroperitoneal) region and (4) within organs.

Subcutaneous Lipomas

The most frequent site of the simple lipoma is a subcutaneous location It occurs here most frequently in the back of the neck, forearm, and axilla and is seldom found in the face scalp chest,

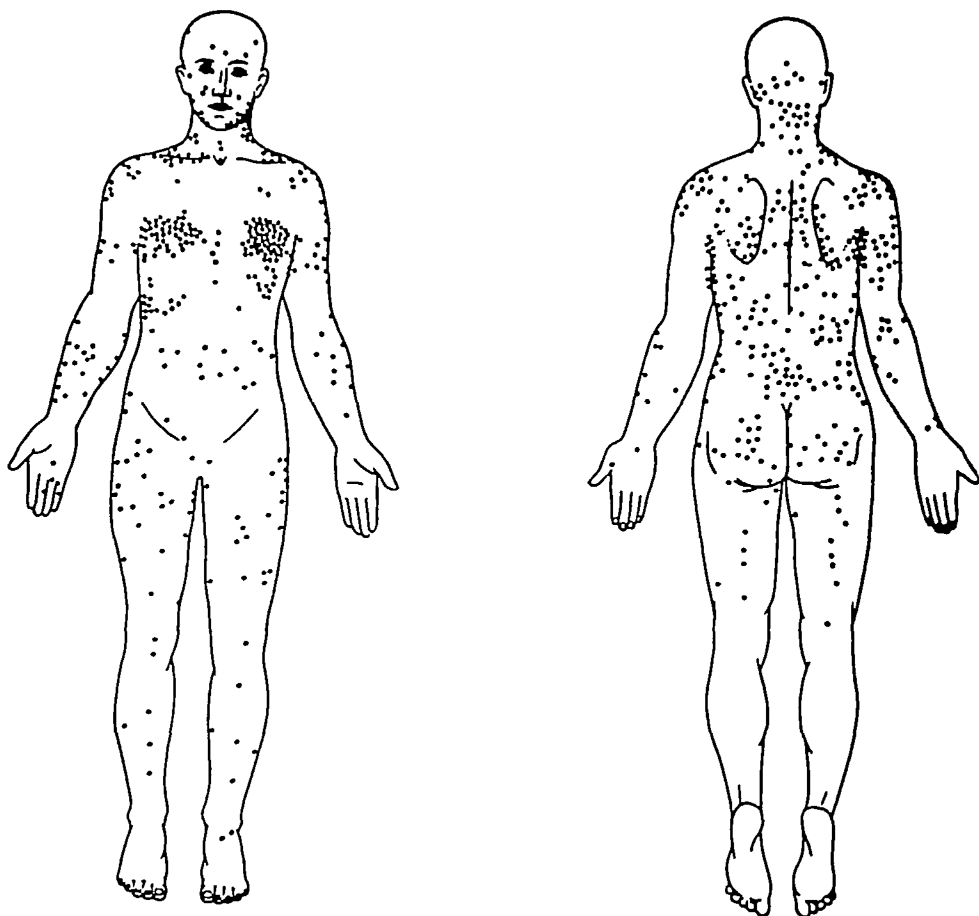


Fig 173 Regional distribution of 352 lipomas in 134 patients (Pack and Pierson, Surgery 36 687, 1954)

inguinal regions, or legs Figure 173 illustrates the distribution of 352 lipomas observed in 134 patients Those which arise from the skin or the subcutaneous regions in certain dependent portions of the body such as the perineum, vulva, or the neck become sacculated and hang like huge fat bags These may sometimes reach such large proportions that they extend from the perineum to reach the ground Subcutaneous lipomas which arise in the axilla are often attached to the overlying skin and are often indistinguishable from axillary breast tissue

Intermuscular Lipomas

A certain amount of confusion exists concerning the exact location of origin of lipomas arising in the depths of the soft somatic tissues They have been referred to as being either intermuscular or intramuscular, and Dege lists some which are submuscular It is difficult to establish the site of origin, as some of these neoplasms may develop within the muscle to extend into the intermuscular spaces and grow expansively in that location From a practical, clinical standpoint these tumors may be listed as intermuscular

They have been recognized for many years Weaver in 1896 reported an intermuscular lipoma which developed in the semitendinous muscle, and Morestin, one year later, described an intermuscular lipoma apparently arising from the gastrocnemius muscle

The intermuscular lipomas are often deeply situated but can be readily identified by soft-tissue roentgenography They appear as translucent encapsulated masses, because of the low specific gravity of fat, this radiolucency is specific for the lipomatous tumors and is not confused even with cysts or myxomas because of the greater water content of the latter tumors In the extremities, the deep lipomas may feel soft and



FIG. 174. X ray showing deep lipoma. Note the radiolucency of the lipoma, the result of the low specific gravity of fat, an important x ray diagnostic feature of deeply situated soft part tumors.



FIG. 175. Intermuscular lipoma (arm relaxed)

flat when the muscles are relaxed, and hard and spherical when the muscles are contracted. The diagnosis can usually be successfully established by an aspiration biopsy

These tumors if not completely dissected will tend to recur They frequently grow expansively and are not encapsulated, hence, the fatty offshoots which lead to recurrence following incomplete resection The actual recurrence rate for lipomas of the extremities, however is not great. Bick reported a



FIG. 176. (*Left*) Roentgenogram showing translucency of tumor in Fig 175 (*Right*) Tumor becomes spherical on muscular contraction.

recurrence rate of less than 1 per cent among 162 lipomas which he reviewed Two such infiltrating benign lipomas have been reported from the Mayo Clinic Some may infiltrate extensively (case report No 18)

A rather interesting congenital intermuscular lipoma arises within the inner surface of the cheek, just inside the masseter muscle within the sucking pad These are believed to represent congenital lipomatous rests (fat pad of Bichat)

Deep lipomas which arise from underneath the pectoralis muscle produce a submammary mass and extrusion of the teat

Synovial Lipomas

Lipomas not infrequently occur within the joint capsule, the popliteal space being one of the frequent sites They may arise from within the joint, either as a result of penetrating the synovial membrane or as a result of overgrowth of fat within the intraarticular synovial tissue Extraarticular lipomas occur also in the fat about the knee and the hip joint The lipomas occurring in joints have been labeled *lipoma arborescens* and produce a characteristic treelike growth within the synovial membrane It is necessary to distinguish these lipomas from villus synovitis, an inflammatory overgrowth of synovia Figure 177 shows a palmar lipoma apparently arising from tendon sheath

Neural Lipomas

Lipomas have occurred within the cranium, Ewing quotes Virchow who has described six lipomas of the pia Other instances of lipomas occurring in the nervous system have been recorded They have been described as arising from the meninges and simulating meningiomas They may arise from sites of imperfect ontogenetic development, as in connection with spina bifida, or of imperfect closure of a cranial suture with the production of a hairlike fibrolipoma, as described by Arnold, quoted by Ewing Bassett records a lipoma occurring in the cauda equina Benign lipomas in the lumbosacral region result from mesenchymal proliferative changes and ectodermal inclusion at the time of closure of the neural tube in the embryo These lipomas penetrate the dura and are attached to the conus According to Bassett, the symptoms are produced because the vertebral column grows more rapidly than the spinal cord and the relative cephalad migration of the cord continues until the growth period terminates, at which time the conus rests opposite the twelfth thoracic or first lumbar body He maintains that



Fig 177 Palmar lipoma arising from tendon sheath

fixation of the conus by the congenital lipoma or lipomatous anchor as growth progresses, causes greater and greater traction to be applied to the conus and the cauda equina and ultimately may result in progressive peripheral neuropathy such as disturbance of bowel and bladder function The diagnosis is made by the combined picture of the lipomatous mass in the midline associated with a bifid deformity of the lumbosacral spine Bassett asserts that it is mandatory to mobilize the lipomatous stalk as it traverses the defect in the fascia and to remove the lipoma

Mediastinal Lipomas

Mediastinal lipomas occur not infrequently assume great size and may be diagnosed by typical decrease in the density of the tumor as revealed by roentgenography Four mediastinal lipomas are on file at the Armed Forces Institute of Pathology and about 65 have been reported to date. They may be connected directly with subcutaneous lipomas extend into the cervical region from the mediastinum or extend into the spinal canal producing the hourglass tumor An occasional bronchial lipoma has been reported but most are limited to the mediastinum Kittle Boley and Schafer reported the resection of an intrathoracic hibernoma.

Retroperitoneal Lipomas

Because of the abundance of fat within the retroperitoneal space (perirenal paravertebral, mesenteric, etc) it is not surprising to find tumors of fat origin within this compartment Approximately 350 instances of lipoblastic tumors have been reported in this location of which about one third arose from the perirenal fat The fat tumors of the retroperitoneum are unique in two respects

1 Because they are clinically quiet during their early period of development and because of the nature of this anatomic site, they grow unhampered and attain huge sizes In the classic case reported by Delamater in a 30 year old woman the tumor weighed 170 lbs and the patient weighed 90 lbs

2 The neoplasms of lipoblasts occurring in this location are malignant more frequently than benign in contrast to these neoplasms in other locations At the Memorial Hospital of 10 retroperitoneal fatty tumors only 2 were considered benign

In a series of 43 retroperitoneal tumors of fat reported by DeWeerd and Dockerty from the Mayo Clinic, they observed that the sex ratio was 1.3 females to 1.0 male, whereas in collected series it is 3 females to 1 male The most frequent age bracket was between the fourth and fifth decades Symptoms were ill defined and urography was a great aid in establishing the diagnosis The appalling operative mortality which varies from 11 to 30 per cent, focuses upon the malignant clinical character of this tumor Only about one third of collected series were benign histologically Recurrences have been observed in 70 per cent of the Mayo Clinic group and 60 per cent of those patients operated upon were dead within 5 years after treatment

The reader is referred to Chapter 28 for a more detailed account of retroperitoneal tumors

Bone Lipomas

Periosteal tumors have been described by Ewing, Codman and others Two patients bearing lipomas arising from the periosteum and extending into the contiguous soft tissues have been recorded by Bartlett One arose from the periosteum of the humerus in a 7 year old boy (Fig 178) and the other arose from the posterior aspect of the tibia in a 6-year-old boy



Fig. 170. Familial lipomatosis. Over 400 discrete tumors were surgically excised during two operative séances.

ous, they may become large and confluent, producing a knobby contour of the extremities and trunk that may be quite disfiguring. One of our patients had 400 such tumors and another one had 160, all of subcutaneous location. Because of their symmetrical distribution, they are frequently mistaken for multiple neurofibromas. There are evidences of a peculiar relationship that seems to link these tumors with neurofibromatosis of the von Recklinghausen type. Neerbeck in 1887 cited cases of lipomas in which the tumors contained hypertrophied nerve fibers. Grosch, Madelung, Israel, Baumgartner, Buchterkich, and Bunke have reported multiple symmetrical lipomas associated with local neuropathies, trophic disorders, spinal cord lesions and other nervous disturbances suggesting involvement of the central nervous system. We have often seen neurofibromas and lipomas in the same patient. We have attempted to draw certain clinical analogies between multiple lipomas and multiple neurofibromas, as follows:

Both are of multicentric origin. The symmetrical distribution of both groups of tumors suggests a disturbance or defect of the central nervous system as a causative factor. The multiple lipomas and neurofibromas have similar regional localization; for example, on the neck, arms, sides, back, and scapular and gluteal regions. Both groups of tumors are classified as intracutaneous, subcutaneous, fascial, and visceral in location. Multiple lipomas and neurofibromas may coexist in the same individual. The flat, coffee-colored, pigmented areas of skin which constitute one of the signs of von Recklinghausen's disease are often of undisputed hereditary or familial influence in the multiple lipomas are

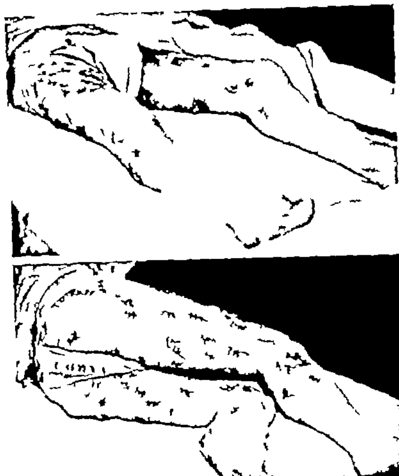


Fig. 180 Familial lipomatosis. Postoperative photograph of patient in Fig. 179 after first of two surgical procedures.

ensory and trophic disturbances, such as hyperesthesia, pain hypesthesia and atrophy of the skin are associated with both tumors (See case report No 19)

Pain may suddenly develop in one of the lipomas (lipoma dolorosa) and will gradually extend to involve more and more of the discrete lipomas. This syndrome of painful lipomas is not related to Dercum's disease (adiposis dolorosa) described later in this chapter

III CONGENITAL, DIFFUSE LIPOMATOSIS

This variety of lipoma is confined to one or two limbs and is usually associated with corresponding enlargement of the muscles and bones of the same limb It may be coexistent with diffuse, cavernous hemangiomas The condition is recognized soon after birth and may show progressive enlargement during infancy and childhood Some of these patients present all the anatomic fea

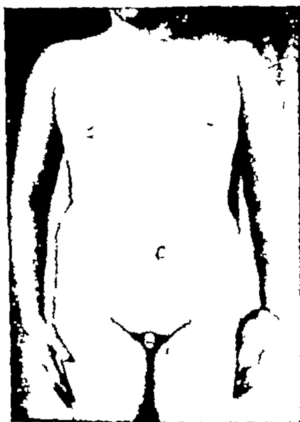


Fig. 181 Froehlich's syndrome. Lipomatosis of left extremity Note enormous macrodactyly (thumb)

FIG 182 Lipomatosis Regional lipomatosis treated by wide surgical excision

tures of Froehlich's syndrome, with or without the attendant symptomatology such as polyuria, renal disturbances, and headache The condition of dystrophia adiposogenitalis, which Froehlich described in 1901, while accompanied in most instances by generalized adiposity, may be associated with tumor formation These tumors are lipomas and may be symmetrically or asymmetrically distributed Other congenital anomalies, such as macrodactylia, may be present (See case report No 20)

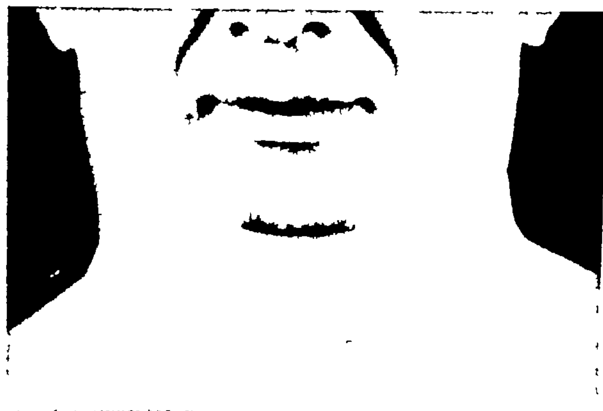


FIG 183 Fat collar of Madelung (fetthals)

The association of overgrowth of bone with these tumors, as shown in two of our patients, is significant The entire extremity may be greatly hypertrophied (See case report No 21) Such lipomatosis involving a single extremity may grow to such gigantic size as to constitute a great physical handicap, because of the weight and discomfort of the enlarged member In some instances, amputation has been resorted to as the only means of relief (Figs 3 and 182)

Another type of lipomatosis which may occur in childhood is the disease



Fig 184. Deep intermuscular lipoma of hip. Soft-tissue roentgenogram demonstrates the comparative lesser density of the tumor

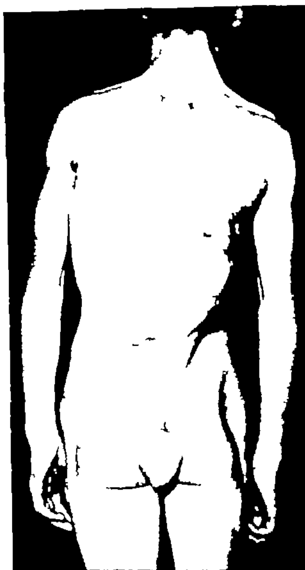


Fig. 185 Congenital lipomatosis invading the sacral and spinal canals and causing partial paralysis. (Case report No. 19)

which Madelung called *fetthals* in which the neck and axilla are symmetrically enlarged. The disease has also been called *adenolipomatosis* since it occurs in the neck, axillary and cubital regions but it really has no relation to lymph nodes.

IV DEGENERATIVE LIPOMA

Tumors of this type do not need separate classification. They represent the large or bulky lipomas which have undergone certain degenerative changes, due to rapid growth and impaired blood supply The xantholipomas and myxolipomas are well known examples They are dangerous because of the occasional conversions into liposarcomas

TREATMENT OF LIPOMA

Lipomas should be excised surgically They are insensitive to irradiation and therefore should never be treated by roentgen ray or radium

All lipomas occurring in children should be excised, as the congenital neoplasms may grow rather extensively Lipomas of the breast should always be removed to establish an exact diagnosis Those of the retroperitoneal region warrant excision because of the huge size which they may attain, to the extent of killing the patient by pressure on contiguous vital structures Mediastinal lipomas should also be excised.

Lipomas arising within muscle tend to infiltrate and should be widely resected. Because liposarcomas tend to occur in the thigh so frequently all fatty tumors of this region should be resected

It is a good policy to remove surgi

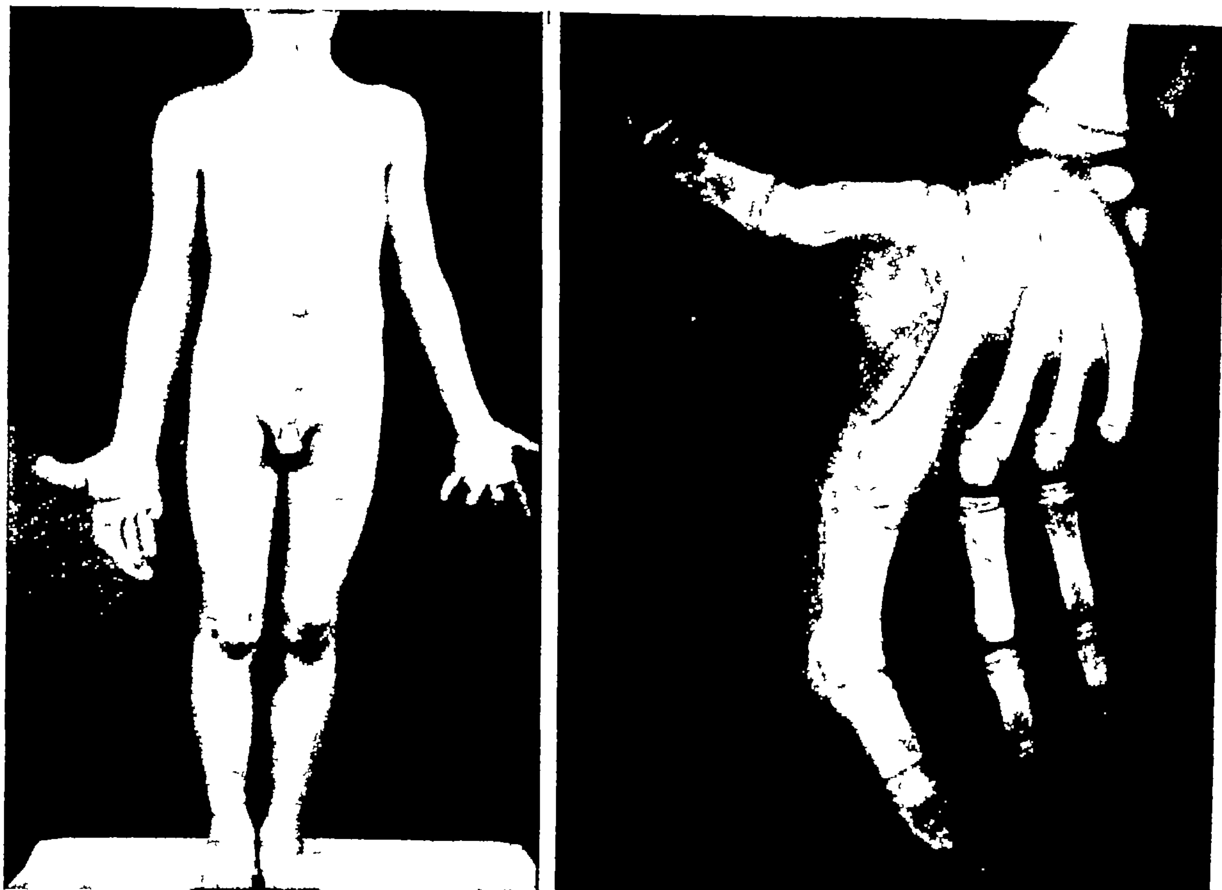


Fig 186 Congenital lipomatosis, macrodactyly

cally all tumors except in those instances where contraindications exist In elderly patients with extensive tumors, treatment may be withheld In patients with metabolic regional accumulations of fat, surgical removal is of no avail and is contraindicated

Diffuse symmetrical or asymmetrical lipomas can be successfully resected Multiple lipomas can be excised (Figs 179, 180) The extent of the operation will depend upon the given situation Certain lipomatous overgrowths produce interesting oncologic and clinical entities Lipomas occur in many bizarre forms and locations, producing various syndromes, a few of which are presented further on in this chapter.

LIPOMAS OF BROWN FAT (HIBERNOMA)

Tumors which arise from a specialized type of fat, which is multiloculated and has a marked vascularity and a high lipochrome content that produces a distinctive brownish coloration, have been described in various animals and man The exact nature of this so-called brown fat however, has remained an enigma It was first described by Belsch, in 1670, who noticed it in hibernating animals It has since been observed in many other animals that do not hibernate Its exact function is not known, but recent interest in this subject has been stirred by Selye and Timiras who have observed anatomic alterations in this fat and in certain fatty constituents of the adrenal glands, with disappearance of the lipid and glycogen granules which occur during stress, and restoration of the lipid and glycogen granules during the stage of resistance

The most comprehensive study relating to brown fat was made by Rasmussen in 1923 He mentioned the various theories that had been promulgated concerning the nature of this fat At first it was considered part of the thymus, later an endocrine gland, then a storehouse for food The most re-

cent theory is a combination of the latter two namely that it is both an endocrine gland *and* a storehouse for food, especially for animals during hibernation. Studies by Rasmussen, however have indicated that brown fat is not an important source of food for the animal when it is hibernating The temperature of hedgehogs has been lowered by Wendt by injecting extracts of brown fat.

Brown fat has been noted in man and some believe that it represents a vestige of the hibernating gland. It has been observed in the human fetus Sutherland, Callahan, and Campbell state that Hatai was the first to describe the brown fat in humans in 1902, that Bonneau in 1888 described it occurring about the shoulders and the neck, and that Shattock proposed that the fat masses in the necks of cretins are enlargements of the hibernating gland This fat is said to arise in the superior mediastinum and, to extend into the neck and axillae, then through the internal mammary vessels and their ramifications into the retroperitoneal region Antopol observed a decrease in the size of the hibernating gland following the injection of cortisone into mice There was also a concomitant decrease in the size of the adrenal cortex.

Hibernomas are rare only 13 have been recorded to date Tumors of brown fat may occur in any of the locations of brown fat but are said to develop most frequently in the interscapular region Some occur in the axilla The recent one reported by Kittle was described in the intrathoracic location.

Brown fat tumors are solitary neoplasms well encapsulated, with a brown hue on cross section. Local resection of this neoplasm results in a cure, with no instance having been reported of a recurrence or metastases Its chief interest is from an ontogenetic and histogenetic viewpoint. One of the most unusual cases, which possibly may have undergone malignant transformation is that reported by Symmers in 1944 in a 3-month-old boy who died of inanition On postmortem examination extensive brownish red nodules were noted disseminated through the abdominal cavity Histologically they resembled the primitive fat organs

ADIPOSIS DOLOROSA (DERCUM S DISEASE)

Dercum in 1888 described a disease characterized by adiposity asthenia, pain, and psychic disturbances. The disease is rather rare, approximately 300 cases having been reported to date. There are some who deny the existence of this as a separate disease entity The fat is distributed abnormally through the body There are usually lumpy encapsulated masses on the thighs, in the abdomen, where they form an overhanging apron, or generalized or diffused over the entire body. In such instances, large masses of fat may hang like sacs from the arms neck, or buttocks. A peculiarity of this entity is the fact that there is rather severe pain associated with the collection of fat. The cause of this pain is not known and even superficial pressure against the fatty masses elicits it. This fact demonstrates that the pain is not due to nerve pressure Rather a remarkable symptom is the attendant severe asthenia. Any exertion and attempt at dieting results in marked and prolonged asthenia. The nature of this asthenia is not known, and there is nothing that one can do to combat it. In later stages of the disease psychic disturbances become manifest.

Various theories have been promulgated to indicate the nature of this entity It may be related to a pituitary disturbance. Some patients with adiposis dolorosa are hypothyroid. The only successful therapy especially of the asthenic phase, has been described by Wohl and Pastor who treated 3 patients

with a combination of aminoacetic acid and prostigmine ammonium bromide. By this measure they were able to place their patients upon restricted diets, thereby causing them to reduce some of the massive weight accumulations They were able to withstand the limited caloric intake only when they were on the regimen of aminoacetic acid and prostigmine ammonium bromide Wohl and Pastor believe that one of their patients had a hypopituitary condition, rare for a patient with adiposis dolorosa, which invoked a hypothyroid state, as shown by a metabolic rate of minus 25 These authors also produced evidence that creatine, which is usually not found in the urine of adults, was present in their patients in rather large quantities, and after the patients were given a regimen of aminoacetic acid and prostigmine there was a marked diminution in the urinary creatine content. In this respect adiposis dolorosa is similar to some of the fibrous dysplasias described in Chapter 15

STEATOPYGIA

This condition is seen in the fat buttocks of the Bushmen and Hottentots Cuvier in 1815 commented upon such a female Bushman who was exhibited as an example of callipygia at the Paris Exhibition in 1815 and described as "the Hottentot Venus" Miller in 1930 described a patient who was an acromegalic and who presented evidences of steatopygia There is no needed treatment, and this situation is mentioned only for its unique interest

CLINICAL MANIFESTATIONS OF LIPOMA: CASE REPORTS

The following case reports illustrate some of the bizarre clinical syndromes manifested by lipomas and methods of their treatment

CASE REPORT NO 18 ROENTOGENOGRAPHIC DIAGNOSIS OF DEEP LIPOMA OF THIGH

N Q, a 68-year-old woman whose previous illnesses were noncontributory, had been aware for eight months of an enlargement of the upper right thigh and groin which she detected when standing in front of the mirror It gradually increased in size without pain or discomfort On palpation there was a mass 8 cm or more in diameter involving the upper right thigh and extending deep into the groin above Poupart's ligament into the iliac fossa The tumor was more easily defined on complete flexion of the knee and hip joint with the thigh upon the abdomen Anteroposterior and anterolateral roentgenograms revealed a sharply delineated region of decreased density in the soft tissues about the proximal right femur, extending from the level of the junction of the proximal and middle thirds superiorly to the level of the acetabulum There was no evidence of bone destruction or production The roentgenographic diagnosis was soft tissue tumor of decreased x-ray density in the right hip region Presumptive diagnosis lipoma

The lipoma was dissected from the femoral trigone and beneath the deep fascia and femoral vessels It was closely approximated to bone and extended into the iliac quadrant retroperitoneally

CASE REPORT NO 19 SACROCOCCYGEAL, LUMBAR, AND RETROPERITONEAL LIPOMATOSIS WHICH PRODUCED SEVERE NEUROLOGIC COMPLICATIONS

M O, a 6½-year-old boy, was first seen in July, 1932 He had a congenital subcutaneous tumor situated over the sacrum and lumbar region to involve the left buttock as well. At both 2½ and 4 years of

age incomplete surgical excisions had been performed in other hospitals On our examination a huge subcutaneous deep lipoma was observed and palpated in the sacrococcygeal region. There was no invasion of the bladder A diffuse tumefaction occupied the lumbar and lower thoracic regions posteriorly and extended high into the left infrascapular region. It extended retroperitoneally to infiltrate the entire muscles of the abdominal wall laterally and to surround the left kidney which was displaced. On radiographic study a scoliosis of the left lower dorsal spine and right lumbar spine was associated with a more or less complete fusion of the vertebrae in the lower dorsal and lumbar spines and increased productive changes in the joints of the lower spine (Fig 185)

During the succeeding 18 years five or six massive resections of the external lipomas were performed, but on each occasion the excision was incomplete On microscopic study the tumor was found typically lipomatous on one occasion remarkable neurogenic elements were visualized that suggested a possible neuroma Dr Frank Foote considered the possibility of hypertrophy of the nerve resembling a glomus structure In other regions there was a poorly formed nest of Pacchionian bodies these were discrete from the lipomatous element.

By the time the patient was 23 years of age he began to experience weakness in his legs Dr Herbert Parsons performed a laminectomy and at the time of the operation found that a bony overgrowth of the lower thoracic and lumbar spine was exerting pressure on the cauda equina nerve roots. In the course of the laminectomy the spinal muscles were found to be widely infiltrated by lipomatous tissue. This patient has a foot drop and other associated neurogenic dysfunctions

CASE REPORT NO 20: CONGENITAL LIPOMATOSIS AND MACRODACTYLIA

S K a 6-year-old boy was born with congenital lipomatosis associated with a macrodactylia involving the right thumb and forefinger and syndactylism involving the middle and ring fingers of the left hand. Two phalanges were missing from the middle and ring fingers of the left hand, and there was a definite scarring following a previous plastic operation for syndactylism. On the right hand the thumb and index fingers were tremendously enlarged, and the lateral aspect of the palm of the hand, including the thenar eminence was increased in size The index finger of the right hand was curved medially so that it could partially encircle the tips of the middle and ring fingers of the same hand. The thumb measured 8 cm in diameter at the proximal phalanx and the index finger measured 8½ cm in diameter The thumb was 6½ cm. in length and the index finger 9 cm. in length Roentgenograms of the hands revealed severe bony deformities characterized by macrodactylia involving the thumb and forefinger with other changes in the metacarpals. The centers of ossification of the carpal bones were delayed in both hands more markedly on the left (Fig 186)

X ray therapy was given to prevent further growth of the bones of the finger and thumb at the epiphyseal lines. The result was cessation of bone growth during the succeeding period of observation of more than 5 years.

CASE REPORT NO 21: SYSTEMIC LIPOMATOSIS

D S a Negro girl, age 6 years was seen October 9 1929 complaining of an enlargement of the entire right arm.

The patient was the eldest of 4 children the other 3 were living and well. There was no history of a similar disease in the family

The patient's birth was normal and she had been breast fed.

The child was considered normal by her parents until she was 1 year old, at which time a ruffling of the skin of the right arm and a small soft tumor on the posterior aspect of the right shoulder were observed This tumor grew steadily and progressed down the arm until finally the entire right upper extremity was involved.

Physical Examination

The child was well developed and well nourished. The pathologic findings were lim



FIG 187 Intussuscepting submucous lipomas of cecum (*Left*) Roentgenogram after barium enema The colon fills well up to the region of the hepatic flexure It was interpreted that a centrally placed mass prevented filling of the right colon, which is distended with gas. (*Right*) Roentgenogram after evacuation of barium enema The mucosa of the distal transverse colon is unaltered but ensheaths the partially obstructed proximal colon and the polypoid mass, which is outlined by a linear deposit of barium (Pack and Booher, S Clin North America *26* 361, 1947)

ited to the local condition The right shoulder girdle and entire right arm were involved in the very soft tumor process which was most prominent on the posterior aspect of the shoulder and elbow The skin over these areas was rough and lymphedematous and contained additional dark pigment The elbow could not be extended beyond 145 degrees No bruit could be heard over the tumor The tumefaction did not increase in size on elevation of the arm The affected arm was almost as strong as the left arm Between the elbow and the wrist there was a large subcutaneous mass with changes in the superjacent skin suggesting keloid formation The two arms were equal in length. The body as a whole, aside from the right arm and shoulder, was symmetrical Circumferential measurements Left shoulder, 25 cm , right shoulder, 31 cm , left upper arm, 17½ cm , right upper arm, 22½ cm , left elbow, 17½ cm , right elbow, 30 cm., left forearm, 15 cm , right forearm, 22½ cm , left wrist, 12½ cm , right wrist, 19 cm , left hand 14 cm , right hand, 16 25 cm

There were no motor, sensory, or reflex inequalities in the two arms There were no significant neurologic segmental clues, except, perhaps, the right scapula, which was smaller than the left X-ray studies of the entire extremity showed considerable enlargement and deformity of the right ulna and lower half of the humerus The radius was uninvolved The tentative diagnosis was symmetrical, localized lipomatosis (See Fig 3)

Treatment

On January 1, 1930, the redundant fat tissue was excised from the extremity by sharp dissection Under the microscope the cells of the tumor were seen to be adult lipocytes with no unusual features The diagnosis was diffuse lipoma

Comment

The fatty tumors in this Negro girl resembled the type of diffuse lipomatosis which Madelung called *fetthals* except that in his description the neck and axilla or

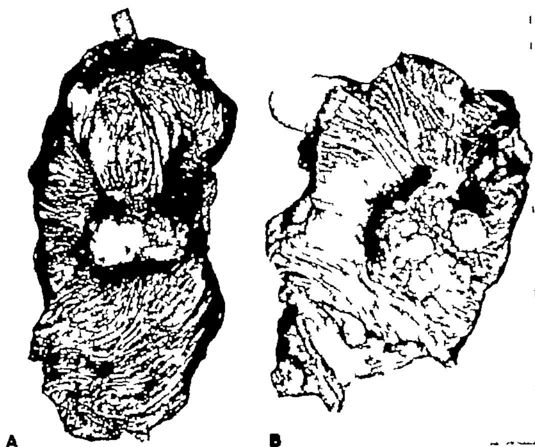


FIG. 188. Intussuscepting submucous lipomas of cecum (two different cases) A. Photograph of resected specimen, showing lipoma arising from a long stalk covered by normal mucosa. B A large, nodular submucous pedunculated lipoma arising from the ileocecal valve. (Case report No 22.) (Pack and Booher S Clin. North America 26 361 1947)

both upper extremities were symmetrically enlarged. This condition has also been called *adenolipomatosis* since it occurs in the neck, axilla, and cubital region, but it really has no relation to lymph glands The brawny thickening in the skin over the elbow and shoulder is due to a type of elephantiasis molle which is found so frequently in patients with neurofibromatosis

CASE REPORT NO 22: INTUSSUSCEPTING SUBMUCOUS LIPOMA OF RIGHT COLON

M F a 41 year-old fur operator had experienced postprandial abdominal pain relieved by alkali or by food for several years Roentgenograms of the stomach were taken and it was reported to be normal Two years after the initial onset of symptoms he developed melena which required hospitalization for 4 weeks and the administration of several blood transfusions. Gastrointestinal x ray series were again reported as normal. Eighteen months later he sustained an attack of bearing-down, in tense abdominal pain associated with con stipation for three or four days. The abdomen became distended and the patient vomited. The attack passed without medi cal attention. Similar episodes occurred *every 3 months, but now* were more severe and finally were recurring at intervals of 2 weeks.

Physical examination revealed a middle-aged man weighing 161 lbs. in apparent good health The abdomen was mildly distended and the stomach dilated with fluid. Sigmoidoscopy revealed only hemorrhoids. Chemical laboratory tests were within normal limits.

X ray study after a barium enema showed a tortuous and greatly dilated

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of soft-part origin James Ewing in 1928 first described a liposarcoma developing in the bone marrow In 1931 his associate, Fred W. Stewart, reported three such cases with characteristic histologic structure and fatal course. The identity of this tumor was challenged by the late W G Barnard, and A P. Stout acknowledged that they do appear different from the liposarcomas originating in other locations

RELATION OF LIPOSARCOMA TO BENIGN LIPOMA

The possibility that malignant lipogenic tumors develop in preexisting benign lipomas is to be admitted, but the majority of liposarcomas undoubtedly occur *de novo*. Lipomas are not seen as a constant accompaniment of liposarcomas There have been two bona fide instances of liposarcomas developing from a benign lipoma (see Sect. I, Chap. 5)



Fig 193 Huge lipoma of the thigh of 19 years' duration Xanthomatous degeneration Liposarcoma developing at superior pole Surgical dissection Late pulmonary metastases (See also Fig 17) (Pack and Pierson, Surgery 36 687, 1954)

CAUSATIVE FACTORS

Liposarcoma can be produced experimentally in laboratory animals, but the cause of these apparently spontaneous tumors in humans remains unknown Haagensen and Krehbiel used 1 2-benzpyrene and provoked one liposarcoma in a mouse and four in guinea pigs The importance of this observation is the evidence it presents that liposarcoma may arise from adult fat cells as a result of prolonged chemical irritation and stimulation James Ewing stated "Since traumatism to fat tissue is often followed by marked proliferation of fat cells and progressive productive inflammation, it is not unreasonable to assume that under special circumstances the proliferation may take on a malignant character." Although Ewing considered trauma a reasonable explanation for the origin of some subcutaneous liposarcomas of the adult-cell type, Stout attributes to injury only a very minor role, which agrees with our point of view

GROSS ANATOMIC FEATURES

The pseudoencapsulation of the average liposarcoma suggests its benignity and tempts the first surgeon unwisely to do a simple enucleation The primary liposarcoma is commonly situated deeply in the intermuscular or periarticular planes rather than in the subcutaneous location The original delimited multilobular tumor lies between, but does not invade, the muscles, this localization may explain the error of [illegible]-

ing these tumors as fascial sarcomas The recurrent liposarcomas do have invasive propensities and infiltrate muscle, fat tissue, and skin. In rare instances, the liposarcomas are of multicentric origin 2 patients in this series had more than one primary liposarcoma The fibrous septa divide the tumor lobules Some liposarcomas are highly pigmented varying from yellow to orange-yellow and even brown, with or without evidence of intratumoral hemorrhage

HISTOLOGIC FEATURES

We shall present two classifications of liposarcoma, as outlined by James Ewing and Arthur Purdy Stout, respectively although the subdivisions are not too dissimilar

A Classification by James Ewing

1 *Adult-cell Liposarcoma* Considered to "represent a lawless phase of growth of fat cells observed in lesser degree in chronic inflammation of fat tissue." The neoplastic cells were thought to be derivatives of adult fat cells, resulting in large polyhedral granular cells, spindle cells and occasional giant cells The granular cells may or may not contain fat droplets These liposarcoma cells become diffuse and appear in many grades of anaplasia. The production of mucous tissue and primary growth of blood vessels is not characteristic of the adult-cell types of liposarcoma

2 *Embryonal Myxoliposarcoma* This tumor simulates the embryonal growth of fat tissue It is associated with a peculiar proliferating capillary vascular system Between the anastomosing vessels are myxomatous tissue and fetal fat cells.

B Classification by Arthur Purdy Stout

1 *Well-differentiated Myxoid Type of Liposarcoma* This tumor resembling embryonal fat is composed of adult fat cells, embryonal stellate cells or spindle-shaped lipoblasts with cytoplasmic droplets staining with Scharlach R or Sudan III. The lipoblasts are usually small but mitotic figures are seldom seen. These tumors may assume bulky proportions.

2 *Poorly Differentiated Myxoid Type of Liposarcoma* A malignant tumor capable of metastasizing and difficult to cure According to Stout, the characteristic cells are bizarre lipoblasts sometimes monstrous, containing misshapen pyknotic or hyperchromatic nuclei

3 *Round-cell or Adenoid Type of Liposarcoma.* The tumor cell is spherical with a central nucleus and abundant foamy cytoplasm containing lipoid.

Ewing described two kinds of fat in the adult, common white fat and the less widely distributed brown fat which he localized as occurring chiefly in the mediastinum, axillae, perirenal region, and about the joints He described brown fat as opaque, highly colored a common component of those fatty tumors designated as xanthomatous Ewing dissected fresh cadavers and amputated limbs in order to study the adipose tissues in the region of the shoulder knee, hip and groin to see whether information so obtained would



Fig. 194 Liposarcoma of chest wall treated by surgical dissection and irradiation, with an 8-year definitive cure. This patient also had numerous subcutaneous lipomas. (Pack and Pierson, Surgery 36 687 1954.)

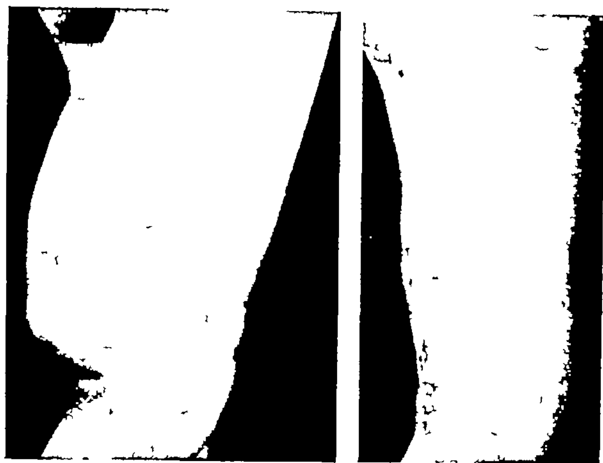


Fig 195 (*Left*) Liposarcoma of thigh, encapsulated, movable, asymptomatic (*Right*) Postoperative state, after radical dissection to include removal of muscle groups (Pack and Pierson, Surgery *36* 687, 1954)

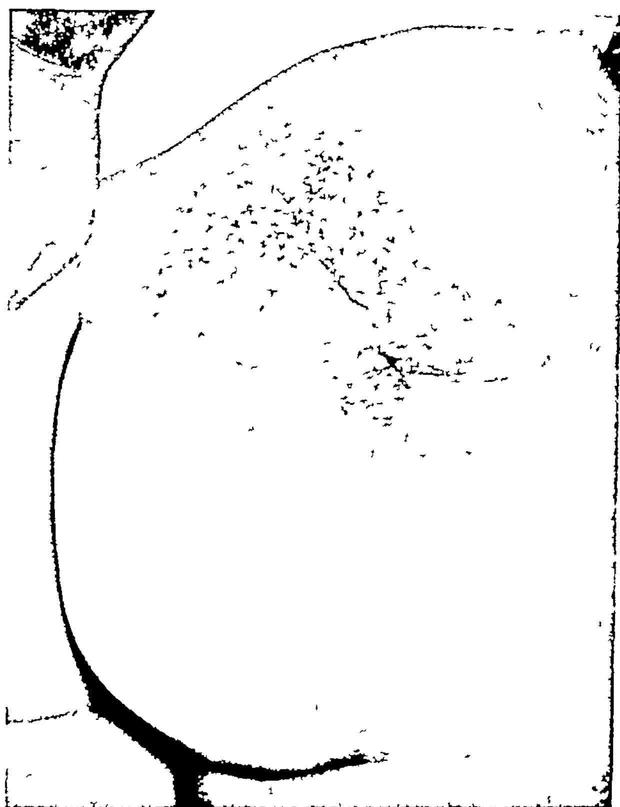


Fig 196 Liposarcoma of buttock, treated by local excision and postoperative irradiation Fifteen-year definitive cure (Pack and Pierson, Surgery *36* 687, 1954.)



Fig 197 Liposarcoma of femoral region, posttreatment state The original sarcoma was fungating, fixed, and inoperable, extending into the deeper iliac quadrant If seen today, it would probably be treated by hemipelvectomy Original treatment by 4-gm radium-element pack, 20 cm radium-skin distance 8 gm-hrs daily total dose—220,000 mgh Six weeks later, surgical dissection and skin graft, later, medial and lateral Kondoléon operations Fourteen-year definitive cure (Pack and Pierson, Surgery *36* 687, 1954)

shed any light on the origin of lipomatous neoplasms in these locations Studies of fetal fat, however, were more productive Ewing found, in the groins and axillae of fetuses, lobulated myxomatous foci amid the so-called brown fat and network of anastomosing blood vessels. He attributed an intimate connection between the capillary vascular network and the growth of fat cells from the mesenchyme He considered the pattern of blood supply in these fetal fat lobules to be similar to that observed in the embryonal myxoliposarcomas

Murray and Stout also studied embryonal lipoblasts as a prelude to the



FIG. 198. (*Top*) Gross specimen of liposarcoma, intact specimen (*Bottom*) Cut section of liposarcoma. Characteristic appearance of tumor tissue (Pack and Pierson Surgery 36 687 1954)

consideration of liposarcomas. To quote them "Fat cells are not just modified fibroblasts but are derived from undifferentiated mesoderm during embryonal life and persist through postnatal life as specialized lipoblasts." They describe the embryonic lipoblasts as of two types (1) widely spaced stellate or spindle-shaped cells enveloped by mucoid intercellular substance, and (2) glandlike lobules of rounded or polygonal fat cells of variable size The cells may contain cytoplasmic droplets of fat.

There are examples wherein one may trace the transformation of a benign myxolipoma to a liposarcoma of low grade malignancy The early phase of liposarcoma may be only foci of nuclear hyperchromatism and gigantism found in the midst of apparently normal lipomatous tissue. One should be suspicious if myxomatous foci or the pres-

ence of fat similar to fetal fat in a lipoma is discovered Myxolipomas with bluish, mucoid matrix and round vesicular cells of uniform size may be diagnosed as benign but unfortunately are prone to recur after simple excision, and the recurrent tumors may then be considered malignant

Murray and Stout have made an important contribution to the accurate determination of the histogenesis of these tumors by employing tissue culture as a diagnostic aid The liposarcomas seldom appear in pure type, this lack of homogeneity is characteristic of this tumor which has a remarkable range of variation in histologic structure Some liposarcomas have almost acellular mucoid pools interspersed in the network of anastomosing blood vessels The lemon-yellow liposarcomas often contain xanthomatous elements and may be only moderately malignant Ewing was of the opinion that the highly pigmented orange-yellow or brown liposarcomas that are very cellular and quite malignant contain very little fat and may have originated from brown fat, especially around joints Ewing also stated that the highly malignant round-cell liposarcomas bear a close resemblance to lymphosarcoma Some liposarcomas also resemble metastatic renal or adrenal tumors to such an extent that erroneous diagnoses occasionally are made. Frozen section and staining with Sudan IV will often demonstrate cytoplasmic sudanophilic globules of variable size The liposarcoma cells are more commonly spindle-shaped or oval, with long cytoplasmic processes and long nuclei containing dark, granular chromatin and one or more nucleoli Degenerating bizarre and multinucleated giant tumor cells are commonly seen on microscopic study Sternberg has demonstrated the extension of the sarcomatous cells along the fibrous septa into adjacent normal adipose tissue and properly offers this as one explanation for local recurrence following conservative removal of these tumors. It may be stated as a general rule that the proportion of cytoplasmic fat globules diminishes with the grade of anaplasia

When the liposarcomas are recurrent or highly malignant they may be so anaplastic that it is difficult to discover any remnants of the tumor that can be identified as lipoblastic Pleomorphism is marked The pathologist may need to consult the primary tumor before he can determine the histogenesis of the recurrent tumor.

SYMPTOMATOLOGY AND DIAGNOSIS

The malignant lipogenic tumor usually starts as an inconspicuous swelling of the soft tissues, exhibiting progressive steady growth without alarming exacerbation until it reaches such proportions as to demand the attention of the patient. The patient's chief complaint is the gradual enlargement of a perceptible tumor

Pressure symptoms may ensue when the neoplasm reaches a certain size, but pain is quite rare at the onset The rate of growth of the liposarcomas shows great variability, *i e*, usually slow, sometimes fast, occasionally quiescent for months or even years, then an exacerbation of growth rate

On the basis of physical examination alone, certain similarities between adipose deposits, benign lipomas, and liposarcomas have handicapped the early recognition and diagnosis of the more important malignant tumor As a general rule, liposarcomas are firmer, less easily compressed and more fixed to underlying tissues, notably fascia, than are their benign counterparts, the lipomas The first evidence of a deeply situated liposarcoma may be only a uniform swelling of a leg or an arm.

Differential diagnosis, using x-ray examination with soft-tissue technic, is helpful but not sufficiently accurate to

insure the benignity of the neoplasm Deep lipomas appear as translucent lobular masses because simple fat tissue has less density than the enveloping soft tissues the liposarcomas, with more fibrous and myxomatous tissue, are relatively more opaque.



FIG. 199 Mesenteric and retroperitoneal liposarcoma. (Pack and Pierson, Surgery 36 687 1954.)

TREATMENT OF LIPOSARCOMA

SURGICAL TREATMENT

The choice between radical surgical dissection and amputation depends on numerous factors such as the degree of malignancy the regional location, the fixity or mobility the primary or recurrent status, the presence of regional and distant metastases and, also important the experience and judgment of the operator

Some liposarcomas are soft, cellular anaplastic, and vascular and sustain at least the reputation of metastasizing with slight trauma. If such a tumor is to be attacked directly by local removal, the dissection should be performed with meticulous, gentle care, and retraction should always be away from, rather than toward, the tumor The soft tissues encompassing the liposarcoma should never be compressed or handled roughly If the neoplasm is on an extremity and the attempt at local removal fails either because of technical difficulties or because the surgeon realizes the futility of the effort, an immediate amputation may be performed above the level of the tourniquet.

If the region of the liposarcoma has been explored but the lesion is not removed, if a formal incisional biopsy has been done, if a previous excision has been followed by recurrent growth of the residual tumor or if the fungation



FIG. 200 Liposarcoma metastatic to heart. Polypoid endocardial metastasis caused valvular obstruction and sudden death. (Pack and Pierson, Surgery 36 687 1954.)

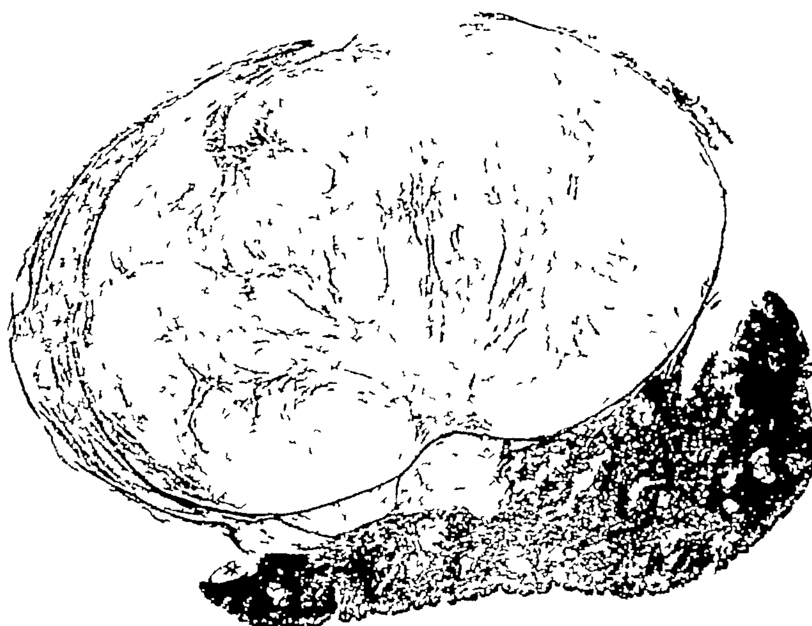


FIG 201 Low-power photomicrograph of transected small liposarcoma, predominantly myxomatous (Pack and Pierson, Surgery *36* 687, 1954)

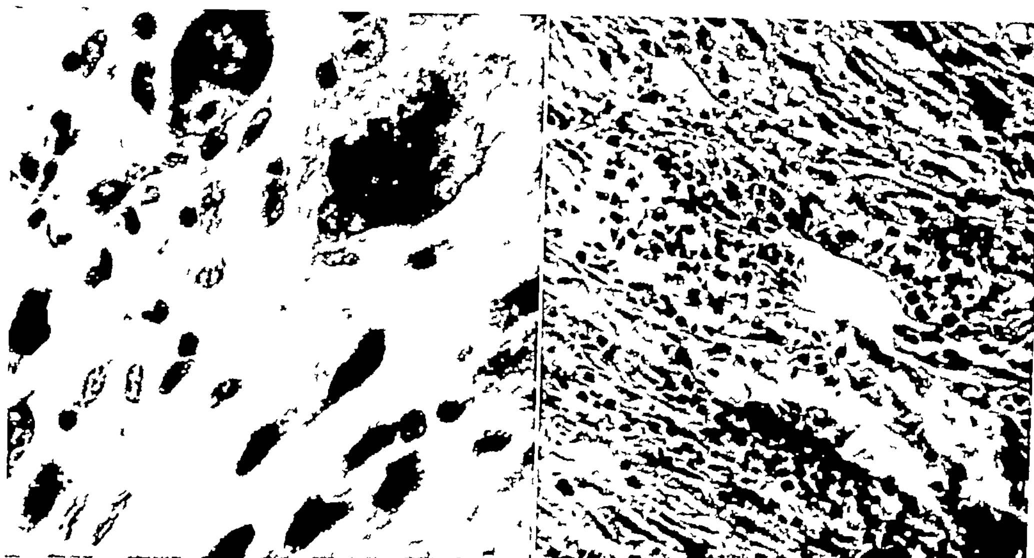


FIG 202 Liposarcoma (*Left*) Bizarre multinucleated giant cells in degenerating liposarcoma (*Right*) More cellular liposarcoma with spindle and spheroidal cells (Pack and Pierson, Surgery *36* 687, 1954)

of the sarcoma has developed through the wound and the surgeon nevertheless decides that he will attempt a radical dissection, the one imperative technical necessity is that a wide encompassing elliptical excision of skin be made far beyond the limits of the original scar Not only the scar in the skin but the scarred tract of the incision down to the tumor must be removed in continuity with the sarcoma because of the very real danger of implanted tumor cells within the previous incision Recurrent liposarcomas may fungate through the operative scar, become infected and necrotic, and even cause death by sepsis Some sarcomas grow under tension within the capsule or pseudocapsule, and a break in this barrier may encourage unrestrained growth of the neoplasm along the cleavage plane of the incision

Although not always possible of achievement, a good rule to follow is to remove the liposarcoma without seeing or encountering it by this we mean



Fig. 203. (*Left*) Photomicrograph of liposarcoma showing a mucoid matrix which stained blue. (*Right*) Low power photomicrograph of myxoliposarcoma. (Pack and Pierson, Surgery 36:687 1954.)

that the investiture of the neoplasm by muscles, fat, and fascia remains inviolate and that the line of dissection is grossly well beyond the palpable limits of the tumor in all directions. Enucleation of the pseudoencapsulated mass leads to recurrence, with the recurrent tumor more cellular, more anaplastic, and infiltrative rather than expansile in growth. The deeper segments of these liposarcomas are usually more adherent. If the tumor lies above the fascia, then the wide excision should include the fascia. In the compromise of selecting local removal over amputation for these malignant tumors, the surgeon should not relax his vigilance in accepting simple enucleation as an easy substitute for the always essential radical dissection. The entire group of muscles involved by or encompassing the intermuscular liposarcomas should be removed from their origin to their insertion. If the sarcoma is on the extremities the order of the dissection is from above downward, *i.e.*, disengaging the superior limits of the tissue dissection first.

If preoperative irradiation has been given, 5 or 6 weeks are permitted to elapse in order for maximal regression to occur and the radiation reaction to subside. Even when the previously palpable liposarcoma has regressed following x ray therapy so that it is no longer clinically apparent, the wide dissection is still done and the date of operation should not be postponed; residual liposarcoma may be found on microscopic study of the excised specimen.

In the case of amputation for liposarcoma, the upper level of severance must be high if not extreme, sometimes requiring fore or hindquarter amputations. The general rule of amputating above the level of origin of the muscle groups involved by the sarcoma is a



Fig. 204. A massive liposarcoma, primary of breast which had produced widespread intraabdominal metastases for which the patient received deep x ray therapy with benefit.

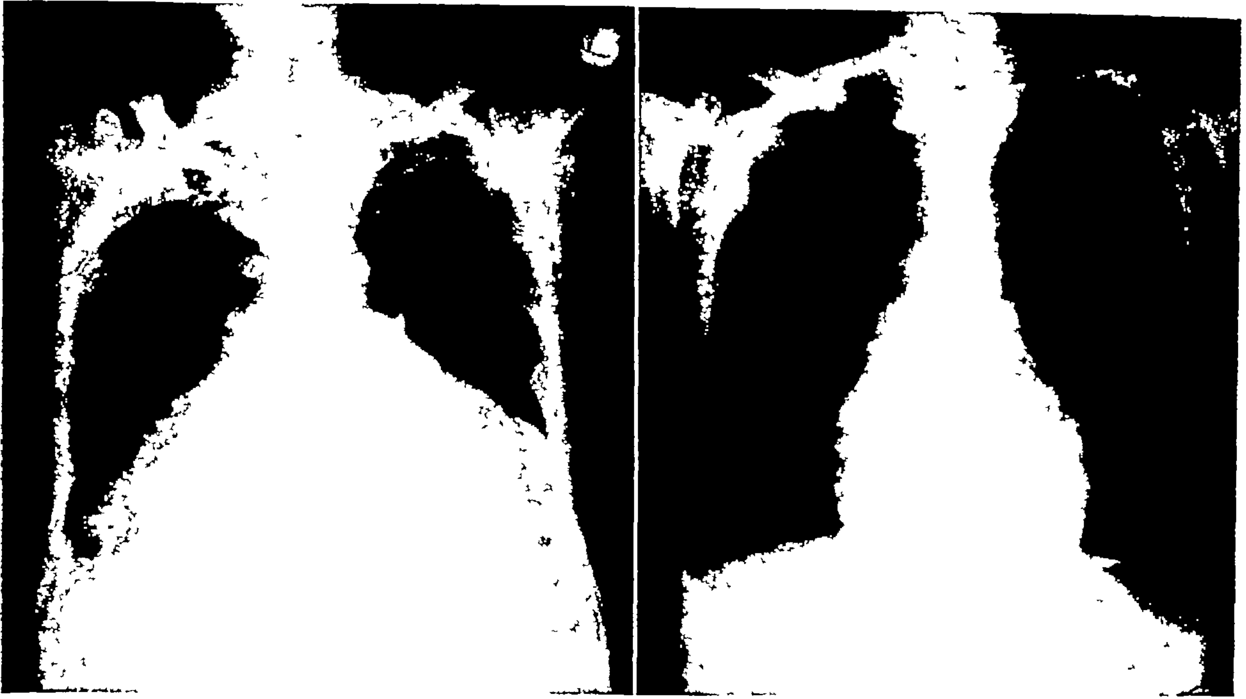


Fig. 205. (*Left*) A diffuse pulmonary metastasis from a liposarcoma primary in the right arm. (*Right*) Roentgenogram of the chest following a course of deep x-ray, with an excellent response.



Fig. 206. Liposarcoma involving the upper thigh, treated by hip-joint disarticulation.

good principle to observe. Amputation may be necessary if there are multiple foci of liposarcoma in the extremity, if the tumor extends indeterminably high along the intermuscular and fascial planes, if it is immovably adherent, especially to important structures, or if it invades bone. Invasion of bone results in subperiosteal and intramedullary extension of the sarcoma superiorly and inferiorly; therefore, amputation through or above the joint with which the affected bone articulates is indicated.

Radiation Therapy

The embryonal myxoliposarcomas are known to be very radiosensitive. This susceptibility may be due in part to the fine capillary blood vessels in the stroma which are easily damaged by irradiation. Recurrent liposarcomas, although more cellular and anaplastic, are sometimes less radiosensitive because their blood supply is obtained from peripheral sources and not from one central vascular system, as Ewing described for



Fig. 207



Fig. 208.

Fig. 207 Liposarcoma, recurrent, of the left anterior thigh. Treated by deep x ray therapy and surgical removal.

Fig 208 Liposarcoma. Clinical appearance of patient in Fig. 207 4 months after treatment. The patient remained asymptomatic for 13 years when he developed lymphatic leukemia and succumbed.

the primary tumor It is our opinion that the occasional infection of the recurrent liposarcoma and its invasiveness are the factors more influential in causing these neoplasms to lose their susceptibility to irradiation. The radiosensitivity of these *liposarcomas is greater than their radiocurability; e g., of 12 liposarcomas* treated entirely by irradiation only 2 (16 6 per cent) were sterilized one of these patients has enjoyed a cure for more than 10 years (Table 46)

regression of the tumor occurred, and in 15 per cent the liposarcomas underwent complete clinical disappearance. *Microscopic foci of residual sarcoma* were found in the majority of surgical specimens subsequently removed. In our group of long term survivals all patients *but one had received radiation therapy* usually as an adjunct to surgery Preoperative irradiation is rarely employed for liposarcomas overlying bone, *e g.*, scalp pretibial region, foot sacrum, etc.

Table 46 Response of Liposarcomas to Irradiation

	Preoperative Irradiation	*Postoperative Irradiation*	*Irradiation Alone*	*Total*
(1) No regression	1	8	4	13
(2) Minimal regression	1	1	1	3
(3) Moderate regression	1	2	1	4
(4) Good regression (50 per cent or more)	1	1	4	6
(5) Complete clinical regression	3	2	0	5
(6) Sterilization of tumor	0	0	2	2
Total	7	14	12	33

Note. Eleven patients received postoperative radiation therapy as a prophylactic measure, no tumor being clinically detectable when treated.

During the earlier years of our experience with liposarcomas, preoperative irradiation was routinely employed subsequent analysis of these cases showed that in 60 per cent of patients a definite

or for those invading bone We have had several instances wherein recurrent or *primary* inoperable liposarcomas have been made technically resectable by preliminary irradiation—for example

in the case of bulky retroperitoneal tumors of this type

We believe that postoperative irradiation is indicated in every instance in which the resected tumor was recurrent The metastases are usually quite responsive to x-ray therapy, particularly in the frequent cases of multiple subcutaneous spherical deposits which are soft, ecchymotic, and very rapidly growing

One patient with multiple bilateral spherical metastases in the lungs, secondary to a liposarcoma of the upper arm, received successful palliative x-ray therapy and is living and well more than 10 years postirradiation

END RESULTS OF TREATMENT

Of the total cases, primary and recurrent, operable and inoperable, under our care since 1928, 67 6 per cent were suitable for surgical resection, i e, operable, of these, 26 7 per cent were primary operable and 33 3 per cent were recurrent operable However, in the more recent period 1944–1948, inclusive, the operability rose to 83 3 per cent of all cases, of which 23 3 per cent were primary and 60 per cent were recurrent operable On the contrary, liposarcomas suitable for palliative treatment, i e, inoperable, decreased from 45 per cent (1928–1933) to 16 7 per cent (1944–1948) The greatest number of inoperable liposarcomas surprisingly occurred in the thigh, next locations in order of inoperability were those on the chest wall, back, and abdomen (retroperitoneum) (Table 47)

Of the 105 patients with liposarcoma, 14 were classified as indeterminate or unsuitable for analysis because they refused treatment or had their therapy elsewhere Of the 91 determinate cases, 27 patients were treated within the past quinquennial period, leaving 64 patients treated more than 5 years ago (the

TABLE 47 OPERABILITY OF LIPOSARCOMA ACCORDING TO YEAR OF ADMISSION

Type of Case	*Total Cases*		*1928–1933*		*1934–1939*		*1939–1943*		*1944–1948*	
	Number	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*
Total cases	105	100 0	20	100 0	34	100 0	21	100 0	30	100 0
Cases receiving definitive treatment	71	67 6	11	55 0	19	55 9	16	76 2	25	83 3
Primary operable cases	28	26 7	5	25 0	9	26 5	7	33 3	7	23 3
Recurrent operable cases	35	33 3	4	20 0	7	20 6	6	28 6	18	60 0
Cases receiving prophylactic postoperative x-ray therapy (surgery elsewhere)	8	7 6	2	10 0	3	8 8	3	14 3	0	0 0
Cases receiving palliative treatment or none	34	32 4	9	45 0	15	44 1	5	23 8	5	16 7
Primary inoperable cases	9	8 6	1	5 0	5	14 7	1	4 8	2	6 7
Recurrent inoperable cases	19	18 1	7	35 0	8	23 5	2	9 5	2	6 7
Cases refusing treatment	6	5 7	1	5 0	2	5 9	2	9 5	1	3 3

determinate group) Of these 64 patients 2 are now living with recurrent sarcoma, 39 are dead of liposarcoma (failures) and 23 (35.9 per cent) are living and well (definitive cures) Eight of these patients have been cured for more than 10 years (Table 48)

TABLE 48 LIPOSARCOMA: FIVE YEAR END RESULTS

Total cases				105
Indeterminate cases (cases refusing treatment, not completing treatment lost track of or treated elsewhere)				14
Determinate cases (total to date)				91
Determinate cases, recent (less than 5 years)				27
Determinate cases suitable in time for evaluating 5-year cures				64
Failures, died with liposarcoma				39
Living without sarcoma under 5 years after treatment for recurrence				2
Successful results, without sarcoma 5 years or more				23
5–10 years	15	Primary operable cases	12	
10–15 years	7	Recurrent operable cases	4	
Over 15 years	1	Prophylactic x ray therapy	7	
Five-year-cure rate				
Successful results divided by determinate cases				23/64 (35 9 per cent)

The end results based on the location of the tumors do not show too great a variability with the best rates for cure occurring for those liposarcomas of the arm (55 6 per cent) and foot (50 per cent) and the lowest rates for those on the buttocks (25 per cent) and groin (25 per cent) (Table 49)

The end results based on the type of treatment are compared with the over-all curability of 35 9 per cent. Those liposarcomas treated by local excision and postoperative x ray therapy had a five-year-cure rate of 87.5 per cent, due to the very early and favorable stage of their growth. Radical surgical dissection resulted in a 66.7 per cent five-year survivals without recurrence, which is better than the cure rate following amputation (33.3 per cent) because in past years amputation was reserved for the very advanced cases (Tables 50 and 51)

CASE REPORT NO 23: QUESTIONABLE TRAUMATIC ORIGIN OF LIPOSARCOMA

A. B a 34-year-old white, single female schoolteacher was admitted to Memorial Hospital on May 31 1937 In September 1936 while riding a mule on her vacation, she was thrown, and the mule stepped on her upper inner left thigh The mark of the mule s hoof was seen on the skin at the time of the injury lacerating the thigh. A slight, tender swelling appeared beneath the site of the injury but gradually disappeared following the application of heat. This was diagnosed as a hematoma. There was however a residual scar in the skin at the site of the injury and dimpling of the skin over an underlying nodule The thigh which had been swollen from the hip to the knee regained its normal size She was well enough to engage in winter sports such as skiing and skating, and in March, 1937 had a general physical examination, at which time no residual abnormality in the injured thigh was found. Later that month she noticed a reappearance of the mass at the site of the injury It gradually increased in size until May 1937 when a local excision was attempted in a Western hospital. The tumor was found to be situated in the left thigh in the region of the left femoral trigone It was described

TABLE 49 LIPOSARCOMA LOCATION OF TUMOR IN RELATION TO FIVE-YEAR SURVIVAL WITHOUT SARCOMA

Location of the Tumor	*Cases Available for 5-yr Analysis*			*5-yr. Survivals*		*Distribution of Determinate Cases*						
				(Percentage Based on Determinate Cases)		*Primary Operable*		*Recurrent Operable*		*Prophylactic Irradiation*		*Inoperable Number*
	All Cases	*Indeterminate Cases*	*Determinate Cases*	*Number*	*Percentage*	*Number*	*5-yr Cures*	*Number*	*5-yr Cures*	*Number*	*5-yr. Cures*	
All cases	75	11	64	23	35 9	19	12	13	4	8	7	24
Hand	0	0	0	0	0 0	0	0	0	0	0	0	0
Arm	12	3	9	5	55 6	2	2	3	1	2	2	2
Shoulder	6	1	5	2	40 0	2	0	2	2	0	0	1
Foot	2	0	2	1	50 0	0	0	0	0	1	1	1
Leg	5	2	3	1	33 3	0	0	2	0	1	1	0
Thigh	30	3	27	8	29 6	9	5	3	1	3	2	12
Buttock	4	0	4	1	25 0	0	0	1	0	1	1	2
Groin	6	2	4	1	25 0	2	1	0	0	0	0	2
Chest, back, and abdominal wall	10	0	10	4	40 0	4	4	2	0	0	0	4

TABLE 50 TYPE OF TREATMENT OF LIPOSARCOMA IN RELATION TO FIVE YEAR SURVIVAL WITHOUT SARCOMA BASED ON DETERMINATE CASES AVAILABLE FOR FIVE YEAR ANALYSIS

Type of Treatment	*Total Cases*			*Primary Operable*			*Recurrent Operable*			*Inoperable Number*
	Total Cases	*5-yr Cures Number*	*5-yr Cures Percentage*	*Total Cases*	*5-yr Cures Number*	*5-yr Cures Percentage*	*Total Cases*	*5-yr Cures Number*	*5-yr Cures Percentage*	
Total cases	64	23	35.9	19	12	63.2	13	4	30.8	24
Excision only	10	5	50.0	5	4	80.0	3	1	33.3	2
Excision and irradiation	15	7	46.7	9	5	55.6	6	2	33.3	0
Amputation	3	1	33.3	0	0	0.0	3	1	33.3	0
Dissection	3	2	66.7	3	2	66.7	0	0	0.0	0
Hip-joint disarticulation	1	0	0.0	0	0	0.0	1	0	0.0	0
Prophylactic postoperative irradiation	8	7	87.5	0	0	0.0	0	0	0.0	0
Irradiation only	23	1	4.3	2	1	50.0	0	0	0.0	21
No treatment given	1	0	0.0	0	0	0.0	0	0	0.0	1

TABLE 51 RADICAL SURGICAL TREATMENT OF LIPOSARCOMA

Type of Operation	*Total Cases*	*Indeterminate Cases*	*Cases Treated (Percentage)*	*Cases Treated 5 Yr Earlier*	*5-yr Cures Number*	*5-yr Cures Percentage*
Total cases	14	2	4	8	2	25.0
Amputation	3	—	1	2		
Hip-joint disarticulation	3	1	—	2		
Hemipelvectomy	3	—	3	—		
Groin dissection	3	1	—	2	2	100.0
Axillary dissection	2	—	—	2		

as an infiltrating myxomatous tumor adherent to the femoral vessels. Only a portion of the tumor was surgically removed It was very vascular and bled profusely requiring packing to control the hemorrhage. Following this operation she received three x ray treatments to each of three ports, one anterior one posterior and one lateral, the exact dose was not stated. She was sent across the continent with the packing still in the wound.

Physical Examination

Physical examination on May 31 1937 revealed a well nourished woman in good general health. In the region of the left thigh, over the region of Hunter's canal was a linear wound with the sutures intact the wound was not completely healed and discharged bloody serum There was an indefinite mass, 10 × 12 cm., soft and compressible over the femoral vessels. The

tumor did not seem to extend high in the femoral trigone and the inguinal lymph nodes and femoral nodes were palpable but soft, suggesting adenitis only There was good motor function of the thigh, although some atrophy of disuse The pathologic diagnosis based on the submitted slide was myxoliposarcoma (Ewing).

Summary of Treatment

From June 1 to 19, she received 152,000 mgh of external irradiation over the site of the tumor, applied by a 4 gm radium-element pack at 20 cm radium–skin distance, 8 gm-hrs daily From July 13 to August 13, during a second admission, she received 80,000 mgh to the left groin with the radium-element pack When she left the hospital in June, 1937, there was profuse discharge from the anterior thigh and an intense radiation reaction was beginning On August 9, 1937, she received high-voltage x-ray therapy to the left thigh through two portals, anteromedial and anterolateral, employing the following factors 198 kv, 0 5 cm Cu filter, 70 cm T–S D, 18 × 11 cm field, 250 r daily to alternate ports for a total of 2000 r to each portal At no time during our observation was the tumor locally resectable and in those years we had not started to perform hemipelvectomy for locally nonresectable tumors of this location

Repeated aspirations of the tumor were required owing to the collection of enormous quantities of blood serum On August 12, 1937, the patient complained of pain in the left chest over the eighth rib, this pain was intensified by deep inspiration An x-ray film of the chest two days later disclosed a dense shadow in the right upper lobe, suggesting metastasis A previous film made July 10, 1937, was normal The pulmonary metastases increased and the patient developed strabismus in the left eye on the day of her death, September 11, 1937

Necropsy Report by Dr. Fred W. Stewart

Anatomic diagnosis

1 Liposarcoma of the left thigh
2 Metastases to retroperitoneal and right supraclavicular nodes, lungs, pleura, mediastinum, diaphragm, heart, liver, adrenals, left kidney, and left ovary.
3 Hydrothorax
4 Pulmonary atelectasis, edema, and congestion
5 Myoma uteri

Microscopic diagnosis

1 General liposarcomatosis
2 Persistent thymus
3 Early acute hepatitis
4 Thrombosis of the right adrenal artery

Comment

The postulates governing the possible origin of a malignant tumor following a single trauma seem to have been fulfilled in this case The authentic history of trauma, the physical evidence of injury, such as laceration and ecchymosis, the absorption of the hematoma, the development of the tumor at the exact site of injury, the interval between the date of the trauma and the appearance of the tumor, etc, all are in accordance with the accepted tenets of this theory The authors cannot accept this doctrine of traumatic etiology for sarcomas of the soft somatic tissues, yet there does occasionally occur a case, as related here, wherein the sequence of events would be difficult to disprove

CASE REPORT NO 24
INCIPIENT OR EARLY LIPOSARCOMA

A 47-year-old woman had been aware for 2 months of a tiny, slightly painful subcutaneous lump on the ulnar aspect of the left palm It did not grow in this interval but was a source of constant annoyance because of pain on pressure There was no history of trauma

Physical examination was entirely normal except for local findings There were no enlarged axillary lymph nodes Situated in the subcutaneous tissues of the left hypothenar eminence was a hard nodule, measuring not greater than 0 5 cm in diameter A roentgenogram of the chest was normal

Under local anesthesia the lesion was excised and found to be a firm, solid, apparently encapsulated, subcutaneous tumor, measuring not more than 0 25 cm in diameter It was yellow in color and appeared

to be slightly lobulated. Pathologic diagnosis by Dr Fred W Stewart was miniature myxoliposarcoma Postoperative x ray therapy was given with the following dosage 500 r through a 2 cm. cone twice weekly for a total dose of 2000 r to the operative area, using the following factors 100 kv 1 mm Al filter 20 cm. T-S D There has been no recurrence after 6 years.

This tumor is the smallest and earliest liposarcoma discovered in this series

CASE REPORT NO 25: PALLIATIVE CONTROL OF LIPOSARCOMA FOR TWENTY YEARS

A 46-year-old newsdealer was first seen at the Memorial Hospital on April 21 1933 Four months previously he noticed a small subcutaneous lump near the right elbow It grew rapidly and was not associated with pain nor did it interfere with function. The patient attributed his trouble to an injury sustained 8 months previously when he struck his elbow against the side of a car while throwing papers, although there was no history of ecchymosis

Physical Examination

On the lateral surface of the right arm, just lateral to the antecubital fossa, was a soft part tumor measuring 6 × 5 cm. It was movable and firm with a separate inferior nodule (2 cm) extending from the main tumor A roentgenogram of the chest was normal.

Operation

On July 3 1933 the tumor was dissected under general anesthesia. It was found to lie partially beneath the flexor muscles at the elbow and in the upper arm It lay on some of the larger nerve ramifications along the brachial artery or its bifurcation. Microscopic study of the specimen led to the diagnosis of spindle-cell myxosarcoma lipogenic.

Postoperative Radiation Therapy

Radiation therapy was given to the right epitrochlear region as follows 1200 r to each of two portals anterior and posterior Factors 198 kv 50 cm. T-S.D., 0.5 Cu filter Fields 15 6 by 9 cm. Treatment was given September 18 to 20 1933

Subsequent Course

This patient remained well until July 15 1935 when a recurrent tumor was noted, involving the right cubital region medial to the scar of the former incision. This recurrence was subcutaneous, movable and consisted of a spherical mass about 5 cm in its largest diameter The patient persistently refused another operation until May 3 1936 At that time the tumor was found to be five times the size it was at the time of detection and appeared to be adherent to the bone and displaced the vessels in the cubitus On May 4, 1936 the tumor was again excised. It was found to be intimately attached to the radial nerve just above the elbow The mass lay for the most part beneath and between the superior portion of the group of superficial antebrachial flexors and appeared semisoft and cystic. The distal portion of the biceps and brachialis muscle formed part of the medial boundary superiorly and anteriorly Anteriorly and laterally the tumor seemed to have a definite capsule, it was easily separated from the surrounding muscles. Following this operation the patient received postoperative x irradiation to four ports covering the cubital fossa and the scar for a total of 2500 r to each portal.

Following this, there was no evidence of recurrent sarcoma until July 18 1938 when a tumor mass measuring 10 × 8 cm. and situated in the right lateral thigh, was found. On September 19 1938 it was excised under general anesthesia On exposure the tumor was found to lie under but not invading the fascia lata, it did invade the underlying muscle. It was well encapsulated and measured about 10 × 12 × 6 cm Pathologic diagnosis of the lesion was spindle- and giant-cell sarcoma

The patient did not cooperate in keeping his follow up appointments On August 8 1939 a recurrence was found lateral to the scar on the thigh. It was soft and elastic, and measured about 5 cm in diameter Also in the right interscapular region was a hemispheric mass measuring 4 cm. in

diameter, representing metastasis Accordingly, radiation therapy was administered with a 4 gm radium-element pack, giving 8000 mgh daily at a 10 cm radium–skin distance for a total of 72,000 mgh to the interscapular tumor and a similar dose to the recurrence in the right thigh On September 14, 1939, it was noted that there was complete regression of both tumors

The patient remained in excellent general condition without evidence of recurrent disease as shown by repeated x-ray films of the chest and physical examinations On November 27, 1944, he developed an acute respiratory infection which subsided gradually within 5 to 7 days He noticed, however, severe breathlessness associated with precordial pains and pain in the left lower chest X-ray films disclosed no evidence of pulmonary metastasis, but did reveal pericardial effusion There was no evidence of recurrent liposarcoma in the thigh, elbow, back, or elsewhere The irregularity of the pericardial shadow and the constant bloody character of the pericardial effusion on each pericardicentesis led us to suspect metastatic involvement of the pericardium by the liposarcoma, although no tumor cells were identified in the pericardial fluid The patient was bedridden, almost moribund, and the cardiac tamponade syndrome was not improving until x-ray therapy was given in fractionated doses over the pericardium Improvement occurred immediately and now the patient is well and asymptomatic

Comment

The liposarcoma, primary in the cubital fossa, apparently metastasized to soft parts such as thigh, back, and perhaps the pericardium The disease has been well controlled by radiation therapy This case illustrates well an often-observed course of the disease and a degree of radiosensitivity that is not generally appreciated

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CHAPTER 19

Tumors of Blood-vessel and Lymph-vessel Origin

BENIGN TUMORS

INTRODUCTION

TUMORS arising from blood vessels comprise one of the most frequent groups of neoplasms afflicting the soft somatic tissues Hemangiomas comprise 22 per cent of all benign tumors and 46 per cent of all soft somatic tissue tumors seen in the clinic (Pack and LeFevre) This category includes only those neoplasms whose principal constituent are blood-vessel elements and does not include the great numbers of neoplasms which contain blood vessels, sometimes to a great degree, as the source of sustenance Blood-vessel tumors make up a heterogeneous group of neoplasms with many individual characteristics The vast majority are benign, they occur with great frequency in the very young (congenital hemangiomas), they produce bizarre clinical syndromes (systemic hemangiomas, Sturge-Weber's syndrome), and certain of the malignant tumors can be rapidly fatal but appear innocuous at the time of onset (Kaposi's disease)

CLASSIFICATION OF TUMORS OF BLOOD VESSELS

Capillary hemangioma
- Simple type
- Port-wine stain
- Spider nevus
- De Morgan spot
- Sclerosing hemangioma

Granulation hemangioma
- Pyogenic granuloma
- Granulation-cell sarcoma

Cavernous hemangioma
- Superficial type
- Visceral type

Hypertrophic hemangioma
- Simple type
- With metaplastic elements

Cirsoid or racemose hemangioma
- Arteriovenous fistula

Systemic hemangiomatosis or hemangioma unius lateralis
- Congenital
- Acquired

Hereditary hemorrhagic telangiectasis (Rendu-Osler-Weber's disease)

Congenital neurocutaneous syndromes associated with angiomatosis
- Von Recklinghausen's neurofibromatosis and angiomas of the skin
- Bourneville's syndrome with tuberous sclerosis, Pringle's disease, and regional angiomas
- Sturge-Weber's disease, encephalofacial angiomatosis
- Lindau-von Hippel's disease, he-

mangiomatosis of retina and cerebellum
Maffucci's syndrome (dyschondroplasia and hemangiomatosis)
Hemangiopericytoma
Benign glomus tumor (Masson)
Malignant type (Stout's tumor)
Special regional hemangiomas
Orbit and eye
Brain
Tongue
Gastrointestinal tract
Liver
Skeletal muscle
Bone
Malignant tumors of blood vessels
Angiosarcoma
Endothelioma
Hemangiopericytoma
Kaposi's hemorrhagic sarcoma

HEMANGIOMA*

Hemangioma is a tumor or autonomous new growth of tissue in which there is a formation of new vessels or proliferation of the vessel walls Sharp distinction must be made between vascular enlargements which are varicosities or aneurysmal dilations of preexisting blood vessels self limited fibroblastic and endothelial hyperplasias as in granulation tissue, and true hemangiomas which are embryonic sequestrations of unipotent angioblastic cells This isolated angioblastic tissue develops from the vascular layer of the mesenchyme and remains discrete and ununited while other normally distributed cells proceed to form the normal blood vascular system The origin, therefore, of hemangiomas can be traced to the failure of these cell groups to establish contact with the developing network of blood vessels, in consequence of which and in their disjointed state, the early angioma does not evolve usually beyond the stage of a mesh of minute, irregular blind channels quite removed from the main, general circulation. The anlage of the angioma is a cluster of solid endothelial cords and islands, which later acquire lumina and form stunted blind capillaries, which in turn later intercommunicate to complete the well-developed hemangioma.

Ribbert strongly opposed the view prevalent in his time, that the tumors arose from preexisting blood vessels which had functioned as such. Ribbert found by interstitial injection that the angiomatous vessels had few or no lateral anastomoses and that the injec



FIG. 209 Hemangioma. Intravascular injection of a radiopaque dye in a diffuse hemangioma of the arm of a 26-year-old male. Note the free vascular anastomosis with adjacent blood vessels.

* In collaboration with Theodore R Miller



FIG 210 (*Left*) Congenital hemangiolymphangiomatosis in a 5-year-old male (*Right*) Appearance 2½ years after surgical dissection of the tumor

tion mass traversed the afferent artery and the efferent vein, but not in the peritumoral tissue He believed that the hemangiomatous varicosities were due to elongation of the vessels comprising the tumor within a more or less closed territory or capsule, without involvement of the surrounding vessels. Ribbert's theory that circumscribed hemangiomas, with the exception of the cirsoid or racemose type, possess only one afferent and one efferent blood vessel and are without anastomotic connections to surrounding blood vessels is acceptable today Hemangiomas bleed when incised, but the surgical removal of the discrete, encapsulated tumors of this type is relatively bloodless surgery, requiring the ligation of only two or three tributary vessels

The resultant tumor may be a simple hemangioma with its encapsulated congeries of modified blood vessels or, in the process of its original sequestration, other mesodermal inclusions may contribute to the ultimate complex structure of the lesion, such as smooth-muscle cells, fat, bone, and the primitive blood islands of Pander As an illustration of this phenomenon, we shall here report the case of a premature infant with multiple hemangiomas, some of which contained definite blood islands forming mature and immature blood cells The nature of the tumor, its complexity, and its distribution in the body may be related somehow to the time period at which the anlage of the angioma develops, *e g*, the hemangiomas with the heterotopic blood islands (See case report No. 26) Again, in the case of the systemic hemangiomas which involve an entire extremity or more, as from finger to shoulder or toe to buttock, the aberrant vascular development undoubtedly occurred at the time the limb budding started, because the hemangiomas in these unfortunate people often incorporate all the structures of the limb, including muscle and bone (See p 105)

GROWTH OF THE HEMANGIOMA

Hemangiomas may remain constant in size or may grow *pari passu* with the child. The embryonal tumor inherits a certain momentum of growth which is usually uncertain but self limited. Once the patient has achieved full size, the hemangioma generally stops growing, with an exception of the cirsoid or racemose type, in which an arterial fistulous communication is prominent. The growth of vessels comprising the neoplasm, both the elongation or varicose enlargements and the saccular or sinusoidal dilatations are markedly influenced by the element of mechanical pressure of the circulation. Therefore, the rate of growth and the structure of the tumor are somewhat dependent on the factor of blood supply to the vessels of the hemangiomas

On occasions hemangiomas have exhibited a startling acceleration in growth rate during pregnancy and less frequently at the onset of menstruation. *The blood volume of the pregnant woman increases by 16 per cent. This increased blood volume has been considered* by some physicians to be the cause of and offers an explanation for the apparent growth and enlargement of hemangiomas during pregnancy One young woman with a huge systemic hemangioma of the shoulder and arm had been treated by vascular ligations and injections of sclerosing solutions, with complete disappearance of the tumor for several years. Pregnancy occurred and the tumor reappeared and rapidly extended to several times its primary size.

INCIDENCE AS TO AGE SEX, RACE, AND LOCATION OF TUMOR

The hemangioma is the most common tumor of infancy and childhood. Three-fourths of these congenital tumors are

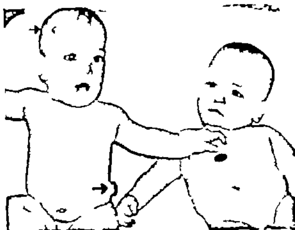


FIG. 211. Hemangiomas in identical twins.

in evidence at birth and the greater part of the remainder make their recognizable appearance in early infancy In one of five patients the hemangiomas are multiple- as many as twenty five have been observed in a single patient. *No explanation is available for the preponderance in females, which is usually at the ratio of two to one. Also* we have observed several instances of their *occurrence in identical twins* (Fig. 211) We have seen few hemangiomas in Negroes

*The majority of recognized heman*giomas are in the skin and subcutaneous tissues. At least 50 per cent of the hemangiomas are situated on the head and neck an explanation probably lies in their development in the region of the embryonal fissures in the face, cheek, lip and neck, and, in fact, they have been designated as fissural angiomas (Fig. 212) As Shaw has said, on the face the tumor may render the unfortunate subject a source of misery to himself or of repulsion to his fellows They occur frequently on the extremities (Fig 213) The location of the tumor in certain special regions such as the retro-orbital space, the breast, the scrotum tongue liver brain, retina, bone, and skeletal muscle, calls for special consideration of treatment, which will be discussed in another portion of this chapter

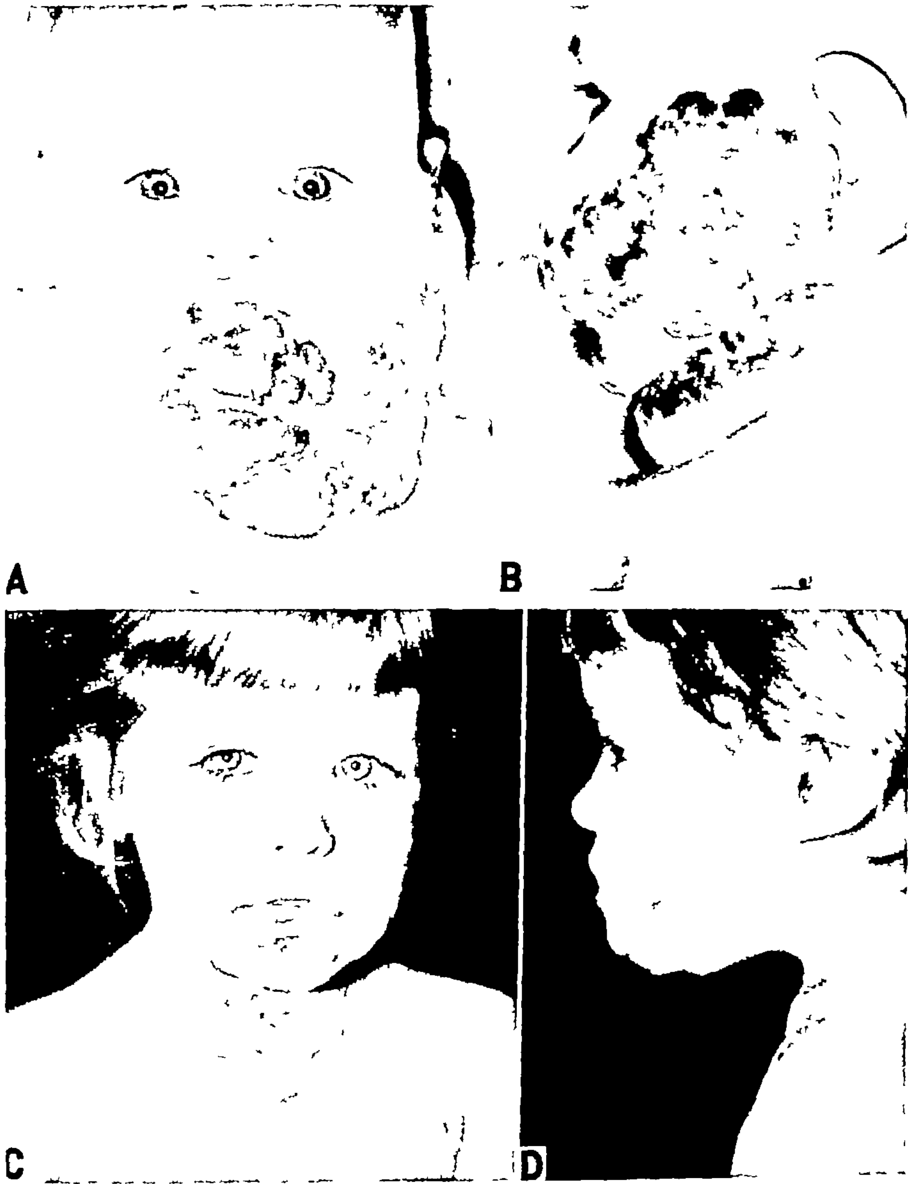


Fig 212 *A, B* Diffuse hemangiomatosis involving the face and neck of a 7-month-old child *C, D* Appearance 4 years later while treatment by sclerosing technic and cryotherapy was still in progress

CAPILLARY HEMANGIOMA

This most common of all hemangiomas occurs in skin and mucous membranes and is of congenital origin, although it may not make its recognizable appearance until variable periods in postnatal life The capillary hemangioma may grow rapidly and varies in size from the minute De Morgan spots (later to be described) to the large, flat port-wine stain The common type, however, is a circumscribed, sessile, lobulated, bright-red tumor The lumina of the vessels comprising this tumor are either empty or contain a few immature or degenerate corpuscles The blood vessels are capillary in type, lined with a single layer of endothelial cells, and surrounded by a reticulum-fiber sheath

Port-wine Stain (Nevus Flammeus)

This pink to purplish, flat, superficial hemangioma is a congenital defect, being noticed at birth and growing with the child The superficial vessels of the derma exhibit diffuse telangiectasia, but no proliferative masses such as are found in the case of other hemangiomas. The purple patch blanches on pressure As the child grows older, the color is more apt to become darker or blue than it is to fade Unfortunately, the face is

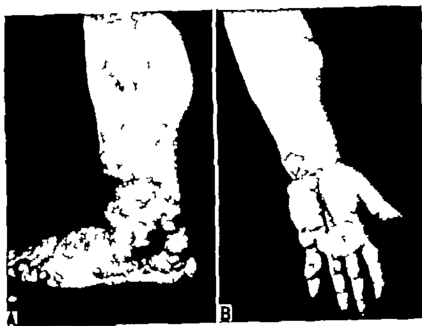


FIG. 213 A. Congenital systemic hemangiomatosis of leg B Hemangiomatosis of hand (same patient)

the most common site, and the mucosa of lip cheek, and oral cavity may be involved in continuity Treatment is disappointing and requires infinite patience and caution. The tumor vessels are not large enough for injection therapy *Irradiation to the face in children is to be condemned.* Freezing produces variable and unpredictable results Cosmetic camouflages such as Cover Mark are clever and very well worth while.

ABRASIVE TREATMENT (METHOD OF JONSSON) Jönsson's method of obliterating the port wine stain is to remove or destroy the capillaries in the surface layer of skin by rubbing the hemangioma with sandpaper or a motor-driven abrasive wheel while leaving the cutis intact. One per cent Novocain solution is used to infiltrate the skin in such a manner that a firm edematous and flat skin cushion is secured. Epinephrine is added to the solution to lessen the degree of bleeding. The rubbing or abrasion must be limited to the confines of the tumor and penetration too deep into the cutis must be avoided, the subcutaneous fat should never be visible One treatment *is usually sufficient* Bleeding is usually profuse therefore compression must be continuously applied. Sterile sulfathiazole dressings are applied, taking proper precaution to prevent the formation of folds of skin, or else coalescences will spoil the cosmetic result. Infection seldom occurs and healing requires an average of 10 days The best results have been obtained if the color of the hemangioma is the darkest possible red with a tinge of blue The abrasive treatment should never be used for cavernous angiomas

TATTOO TREATMENT (METHOD OF CONWAY) Herbert Conway has employed tattooing as a successful permanent camouflage of port wine stains, especially the dermal and subdermal types Conway accredits the use of this method in obliterating birthmarks to Pauli, who in 1935 used tattooing for "congenital purple plaques" of the skin. As Conway has said, the only objectionable feature of the flat port wine stain is its abnormal *color* which varies between red, blue, and purple, depending on the dilatation of the capillaries comprising the angioma, the number of erythrocytes in these vessels, and the degree of oxygen saturation of these cells The basic



Fig 212 *A, B* Diffuse hemangiomatosis involving the face and neck of a 7-month-old child *C, D* Appearance 4 years later while treatment by sclerosing technic and cryotherapy was still in progress

CAPILLARY HEMANGIOMA

This most common of all hemangiomas occurs in skin and mucous membranes and is of congenital origin, although it may not make its recognizable appearance until variable periods in postnatal life The capillary hemangioma may grow rapidly and varies in size from the minute De Morgan spots (later to be described) to the large, flat port-wine stain The common type, however, is a circumscribed, sessile, lobulated, bright-red tumor The lumina of the vessels comprising this tumor are either empty or contain a few immature or degenerate corpuscles The blood vessels are capillary in type, lined with a single layer of endothelial cells, and surrounded by a reticulum-fiber sheath

Port-wine Stain (Nevus Flammeus)

This pink to purplish, flat, superficial hemangioma is a congenital defect, being noticed at birth and growing with the child The superficial vessels of the derma exhibit diffuse telangiectasia, but no proliferative masses such as are found in the case of other hemangiomas The purple patch blanches on pressure As the child grows older, the color is more apt to become darker or bluer than it is to fade Unfortunately, the face is

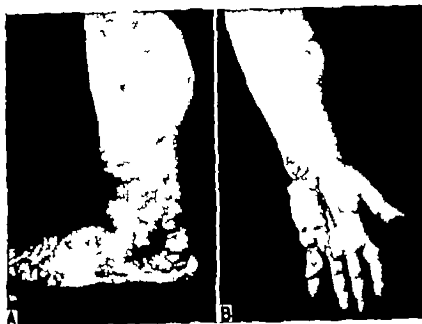


FIG. 213. *A.* Congenital systemic hemangiomatosis of leg *B* Hemangiomatosis of hand (same patient)

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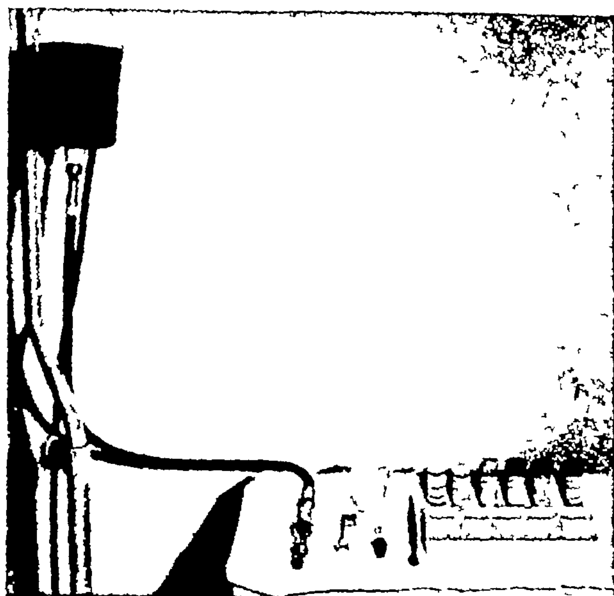


Fig. 214. Tattooing machine and equipment used in the treatment of certain superficial hemangiomas



Fig 215 Clinical appearance of an arterial spider of the infraorbital skin

pigments used by Conway are white (titanium or zinc oxide), yellow (oxide of iron), red (mercury sulfide or cinnabar), flesh color (ferric oxide), blue (cobalt blue), black (black oxide of iron), and green (hydrated chrome oxide) These insoluble pigments are sterilized in 70 per cent alcohol or are autoclaved

The skin is cleansed with a detergent and made antiseptic with Merthiolate The tattooing instrument used by Conway has a cup which feeds pigment paste at a regulated rate into the hollow shaft of 6 parallel needle-holders The rate of oscillation and the depth of penetration of the needles are under regulated control He inserts the needles at an angle of about 6 degrees so as to deposit the pigment particles in an oblique plane at varying depths in the derma White is the basic pigment for port-wine stains and is mixed with a small amount of red or green Conway injects a small region first and observes the color combination three or four weeks later, after desquamation and particle absorption have determined the color change, this enables one to decide on the proper pigment combination Treatments are given every two weeks and the entire course may consume several months The particles used in the tattooing are permanently deposited in the derma Poor pigment retention has been most evident over the lips and nose, but even here good results were obtained The subepidermal type of port-wine stain may bleed profusely and the results of tattooing in this group are not satisfactory. A biopsy is sometimes done to enable the operator to determine the depth of the hemangioma in the skin

Spider Angioma (Nevus Araneus)

The cutaneous arterial spider is a tiny red angioma which owes its descriptive name to its resemblance to a small red spider It has been known by several synonyms—spider nevus, vascular spider, spider telangiectasis, stellate hemangioma, nevus araneus, nevus arachnoides, *tache stellaire, étoile vasculaire.*

William Bennett Bean, who has contributed so much to the knowledge of arterial spiders, has described similar venous structures in the skin which he has called *venous stars*- easily shifting, as he facetiously says, 'from entomology to astronomy" The venous stars develop most commonly when obstruction of the

TABLE 52 DIFFERENTIAL CHARACTERISTICS BETWEEN THE ARTERIAL SPIDER AND OSLER'S DISEASE°

		Arterial Spiders			
	Osler's Disease	*Liver Disease*	*Pregnancy*	*Normals*	*Deficiency Disease*
Familial history	+	±	?	Often +	Often +
Hemorrhage from lesions	+	Rare	Several instances in this series Not cited in literature	Rare	Rare
Age at appearance	In most cases, 20–30 yr	During disease, usually at time of relapse or exacerbation	2nd–5th month	At birth and puberty	Any time
Morphology	Punctiform, more rarely, spider forms	Spider	Spider	Spider	Spider
Pressure in the vessels	Fades partially with 30–90 mm Hg	Periphery fades at 10–20 mm Hg, all but the center fades at 50–70 and disappears at 70–90			
Color	Red purple	Bright, fiery red			
		Center 1–3 mm, area covered by radicles, 1–10 cm			
		1–10 cm	1–5 cm	1–3 cm	1–3 cm
Number (average)	Hundreds	19	7	3	1
Skin temperature	No elevation detected by technic used	Elevated 1°–3° C	Elevated 1°–2° C	Elevated 1°C	Not tested
Distribution	Universal Many in certain exposed mucosal surfaces and in skin	Most on face, neck, arms, and chest Very rare below the diaphragm Occasionally seen in mucous membranes			
Behavior after death	Fade	Disappear	Disappear	Disappear	Disappear
Behavior after hemorrhage	Fade	Fade	Fade	Fade	Fade
Disease of liver and spleen	Infrequent	Usual	Not seen	Not seen	Possible

° After W B Bean The cutaneous arterial spider, Medicine 24 243, 1945

at various pressures and concluded "that the pressure at which blood flows through the vessels of the spider was lower than the systolic pressure of the brachial artery and higher than the subject's venous pressure."

The first historic reference to the vascular spider was probably by Erasmus Wilson, an English dermatologist, in 1869 The association of vascular spiders with diseases of the liver was known more than 80 years ago. Hanot and Gil-

bert, who labeled them *tâches érectiles véritables* observed their relationship to hepatic diseases in 1890 Corbett in the British Journal of Dermatology in 1914 was the first to comment on their *simultaneous* occurrence during pregnancy Our modern knowledge of the cutaneous arterial spider stems from Bean's comprehensive study of 430 persons having these lesions

Bouchard in 1902 first reported on the development of the spider angiomas and their disappearance and reappearance during the clinical courses of cirrhosis and from this observation he stressed the prognostic significance of these lesions in relation to the severity of liver disease Fiessinger noted that the spider angiomas usually disappeared when patients enjoyed clinical recoveries from cirrhosis Loeper Loew Lion, and Netter emphasized the sudden appearances of the vascular spiders as prognostically significant, especially in the cases of cirrhosis associated with splenomegaly and ascites. They found a high level of tyramine in the blood and ascitic fluid of cirrhotic patients paralleling the development and growth of spider angiomas. When Patek, Post, and Victor studied 63 patients with hepatic cirrhosis they discovered spider angiomas in 48 of these people, an astonishingly high incidence. To quote Osler "In cirrhosis in cancer in chronic jaundice from gall stones, spider angiomata may appear on the face and other parts" In fact, these spiders may occur in the presence of various hepatic diseases such as cirrhosis (Laennec's) cardiac cirrhosis, hemochromatosis fatty liver hepatitis, or catarrhal jaundice Few hypotheses have been offered to explain this relationship to liver diseases It has been asserted that an increase or qualitative change in circulating estrogens has caused this vascular phenomenon because of liver impairment and consequent inability to balance the metabolism of ketosteroids

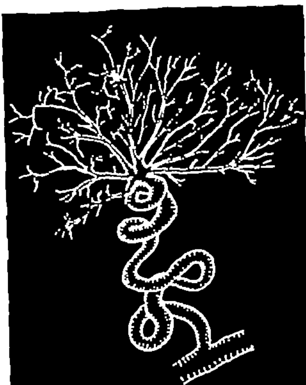


Fig. 217 Schematic drawing of a vascular spider showing the coiled artery the central boss, the branches (some of which end in secondary knobs) the anastomoses between branches and other details. The coiled artery is disproportionately large. (*Courtesy* Dr William B Bean and Medicine 24 243, 1945 Williams & Wilkins Company)

Avitaminosis particularly a deficiency in vitamin B has been considered a provocative cause of spider angiomas, but the relationship has been difficult to prove. Certainly the incidence of spider angiomas with the states of vitamin deficiencies is much lower than for hepatic diseases. The arterial spiders also are said to be smaller in size and of different distribution, occurring more frequently on the hands and arms and seldom on the trunk.

In pregnancy they may occur and grow then disappear after the pregnancy has terminated (Corbett) Bean reported on the occurrence of arterial spiders in 41 women who were pregnant the patients observed them some time between the second and fifth months of gestation. (See Fig 217) They enlarged until term and then disappeared during the period of uterine involution. Bean also studied two patients whose arterial spiders increased

in size 3 days before the menses and remained large for 1 or 2 days during the period of menstrual flow

The cutaneous arterial spider angiomas are found in other relationships which probably have the same etiologic background They develop frequently on the toper's nose They occur in certain males with gynecomastia (probably a common hepatic-estrogen basis) They are seen in patients with paper-money skin (acrodermatitis chronica atrophicans) They are associated with "liver palms" (Perera) in which the thenar and hypothenar regions, finger pads, and bases of nails show a mottled, cyanotic erythema, occurring usually in women and especially during pregnancy Invariably the arterial spiders completely disappear on the death of the patient, in fact, that they are impossible to find after death is in keeping with their arterial structure

If treatment is chosen to be done, the lesion is quickly obliterated by simply touching it with the blunt end of a large needle heated to a dull red color or by electrodesiccation using a monopolar Oudin current

De Morgan Spots

These tiny, smooth, pink flecks occurring in middle and later life on the trunk and face are perhaps only small endothelial cell rests They are said to be

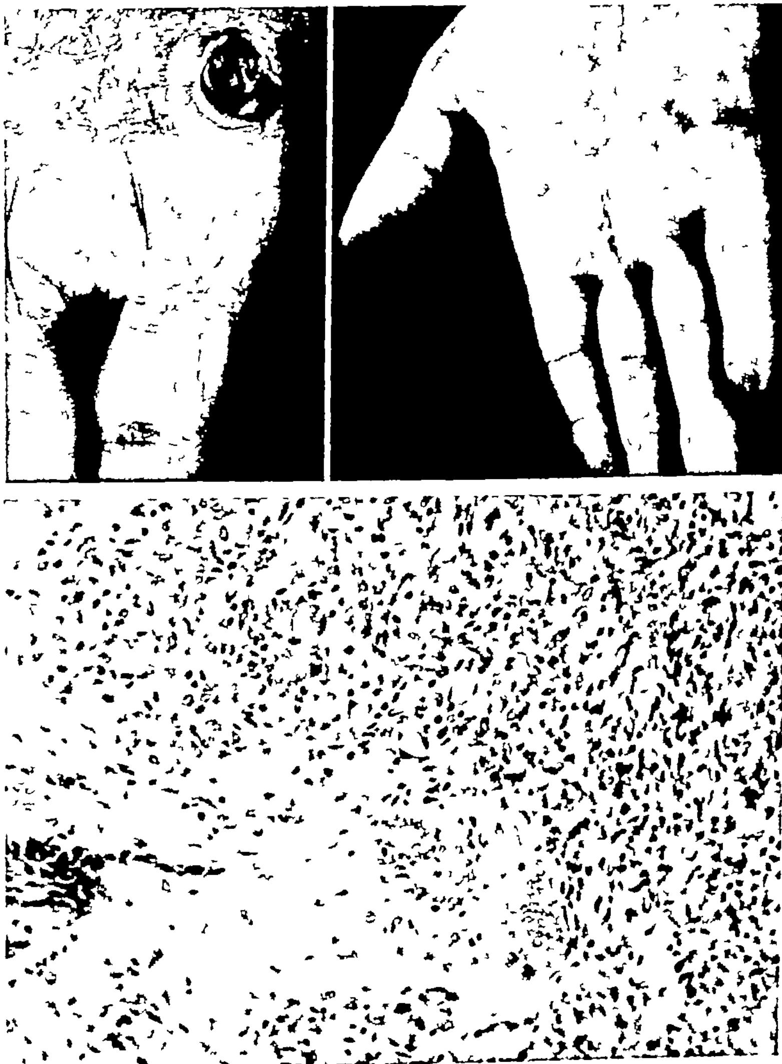


Fig 218 (*Upper left*) Granulation hemangioma of hand (*Upper right*) Appearance after radiation therapy (*Lower*) Microscopic appearance of a granulation hemangioma Note the numerous capillaries and the inflammatory type reaction

more frequent in patients with hepatic cirrhosis.

SCLEROSING HEMANGIOMA

Connective-tissue proliferation has been so great that the perivascular and endovascular thickenings form a solid mass in which the lumina of the major ity of blood vessels are often invisible. Some capillary vessels are visible, and scattered throughout the tumor may be seen phagocytes containing hemosiderin and lipoids. The tumor is firm and non compressible and bears some microscopic resemblance to the benign der matofibrosarcoma protuberans

GRANULATION HEMANGIOMA

Granulation hemangioma, sometimes called *pyogenic granuloma* is exuber ant proud flesh which consists of sprout ing capillaries usually under the intact epidermis or mucous membrane. It may occur anywhere in the skin although it is more common on the hand, especially the fingers. It may develop as multiple growths from the gingivae during preg nancy In most cases, the etiology is obscure, but the tumor may spring from a small puncture wound. The lesion is es sentially an infectious granuloma. Stout has described the structure as composed of stemmed vessels with capillaries sprouting circumferentially to form mi croscopic lobules The base is sometimes sessile, but occasionally it is peduncu lated, with a minute stalk. Simple sev erance through the pedicle seldom suf fices for treatment and the small funga tion may recur almost overnight. The tumor is at times alarmingly vascular and bleeding may be difficult to con trol. Circumferential excision of the base with suturing or topical application of radium or contact x ray therapy is uniformly successful. This granuloma is radiosensitive. The name *pyogenic granuloma* is a misnomer since infection is not grossly present.

CAVERNOUS HEMANGIOMA

The blood vessels become much more dilated than in capillary hemangioma This physical characteristic is due to an expanding connection between the general circulation and the channels of the fundamental capillary hemangioma, so that the capillaries become distended and form pools or sinuses These spaces are limited by thin septa and form spherical sacculations or cul-de-sacs in which the circulation is sluggish. The entrant vessels are larger than in the capillary hemangioma. These tumors are soft and readily compressible. They ex tend into the subcutaneous tissues Vis ceral hemangiomas of the liver and gas trointestinal tract are usually cavernomas Depending on their vascular con nections and location, they may reach enormous size and exhibit aggressive growth.

HYPERTROPHIC HEMANGIOMA

This tumor is the benign analog of the malignant hemangioendothelioma. It is a solid, noncompressible tumor of variable hue, usually purplish-red. The endothelial cell is the neoplastic unit and the overgrowth of these endothelial



FIG 219 Large cavernous hemangioma involving the major portion of the posterior wrist and forearm.

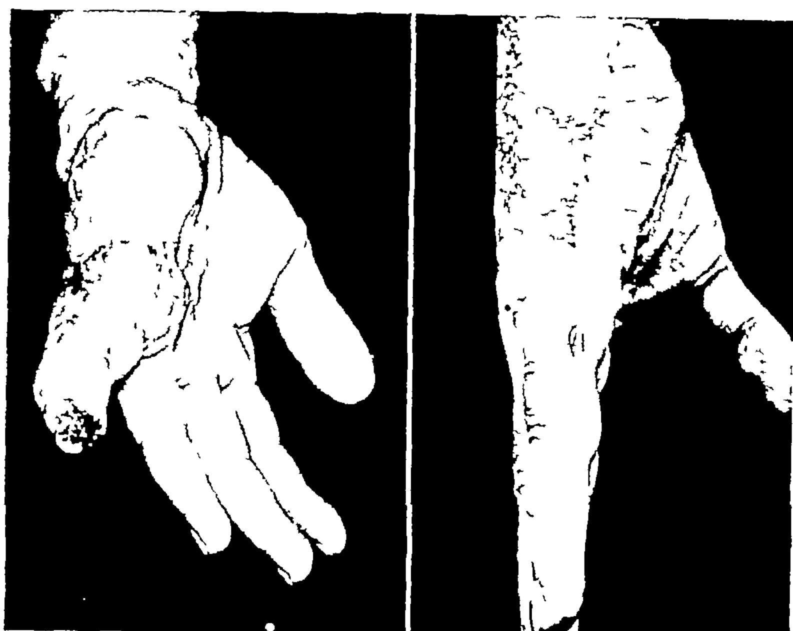


FIG 220 (*Left*) Cirsoid or aneurysmal angioma, arteriovenous fistula, involving hand and little finger (*Right*) Clinical appearance after amputation of digit and partial amputation of hand

cells tends to obliterate the lumina of the blood vessels These neoplasms are not well localized, are often locally aggressive, and tend to recur after operation Although they are of hemangiomatous origin, they are solid tumors and never undergo spontaneous retrogression The injection of sclerosing fluids is futile and the tumors are radioresistant Complete surgical excision is the treatment of choice

RACEMOSE OR CIRSOID ANEURYSMAL HEMANGIOMA

The arterial racemose hemangioma develops *de novo* or through the transformation of a preexistent quiescent hemangioma such as the port-wine stain The essential or distinguishing feature is the size of the arteriovenous fistula, which may gradually become evident or have a surprisingly sudden onset, chiefly in adults Most cirsoid hemangiomas are located on the face or neck and have close vascular connections with branches of the carotid artery Virchow described the tumor as resembling a pulsating mass of earthworms due to the clinical appearance of the dilated, tortuous, and throbbing vessels Just as with aneurysms, the constant pulsation can erode adjacent bone The tumor may extend over the scalp, erode the skull, penetrate the cranium, and even communicate with the meningeal vessels Surgical excision after preliminary ligation of the arterial supply (in severe cases the external carotid artery) may be feasible If the tumor is inoperable, the communicating artery must be ligated before conservative therapy, such as interstitial irradiation or the injection of sclerosing solutions, is attempted

DIAGNOSIS OF HEMANGIOMAS

Pulsation or coloration of the tumefaction often makes the diagnosis obvious However, because certain angiomas may occur in such unusual locations as the finger (Fig 220) or masquerade as another tumor, a cautious biopsy may be necessary to confirm the diagnosis.

SPONTANEOUS CURE OF HEMANGIOMA

Ribbert long ago demonstrated that spontaneous cure of hemangioma occurs and follows a progressive diminution in

the blood supply to the tumor by a stenosis of the afferent vessels supplemented by progressive fibrous hyperplasia of the stroma, especially at the periphery of the lesion near the capsule Considering how delicate and tenuous this blood supply is, it is surprising that spontaneous regression does not occur more often through the accident of thrombotic occlusion (Fig 222) It has been said that this retrogression of hemangiomas without treatment is often accelerated at the period of the first or second dentition Parents who know of these spontaneous cures have unwisely postponed treatment of their own infants with the result that the hemangiomas have frequently grown larger more aggressive and more difficult to treat The accident of infection is often followed by the happy sequel of spontaneous cure, due to ulceration, thrombosis and consequent obliteration of the vascular

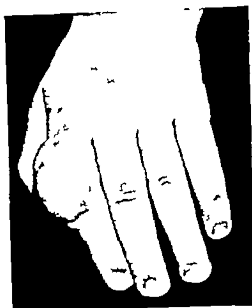


FIG. 221 Cavernous hemangioma of finger

tumor An interesting instance of thrombocytopenic purpura and hemangioma of the forearm with spontaneous cure of the hemangioma is presented in case report No 27



FIG. 222. Spontaneous cure of hemangioma of skin. (*Left*) A female infant born with a congenital cavernous hemangioma involving the entire hand. The dorsum, palm, and intervening tissues were occupied by a huge purple, compressible tumor It involved the base of the fingers and completely encircled the hand. The ulna bone was much longer than the radius because of overgrowth of the former at its distal epiphyseal line a phenomenon common with deeply situated hemangiomas. (*Right*) At the age of 4 months, spontaneous thromboses occurred throughout the tumor which became painful and ulcerated. No direct treatment was given. Within 4 months time the tumor had become completely obliterated.

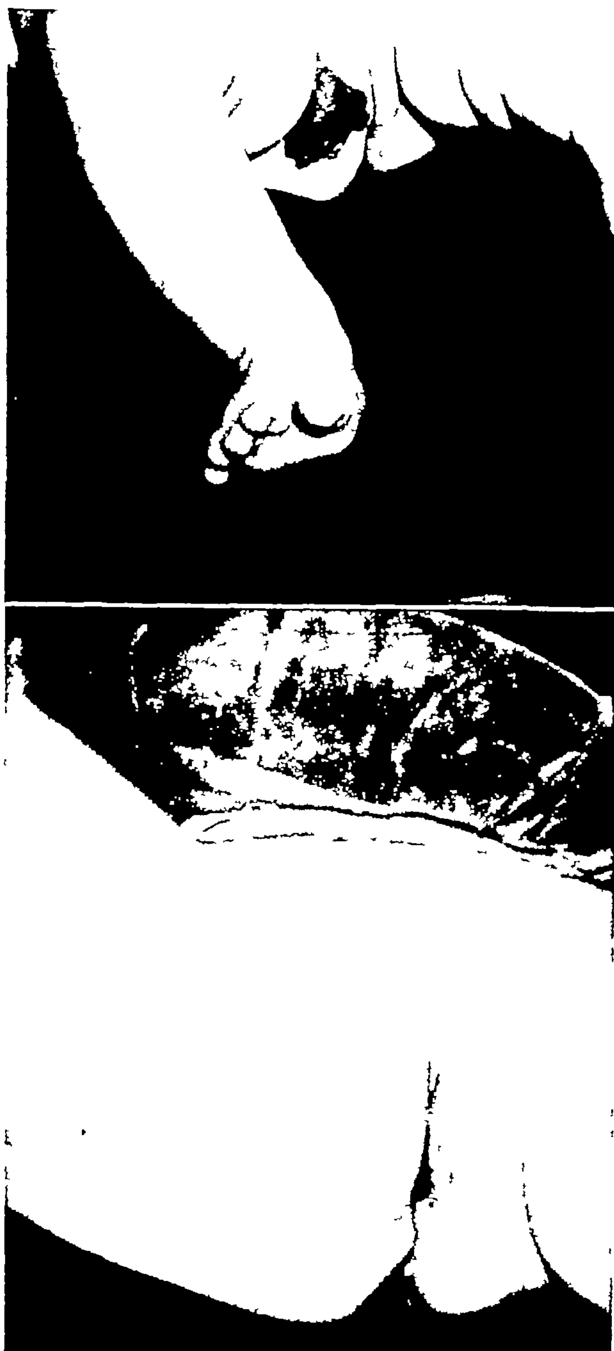


FIG 226 (*Upper*) Hemangioma of vulva in an albino infant (*Lower*) Result after cryotherapy with carbon dioxide snow

thousand hemangiomas The first sclerosing agent probably to be employed was scalding water, this procedure has not been abandoned We have used it with success by employing a thickly insulated syringe so as not to burn the operator Urethane (solution of quinine and ethyl carbamate) is a satisfactory chemical Sodium morrhuate (5 per cent) or Sylnasol is perhaps more universally employed, in quantities of 0 25 to 2 cc These solutions, when accidentally injected without the tumor, do not cause painful necrosis The injection of sclerosing solutions into racemose (cirsoid) hemangiomas, muscle angiomas, and systemic hemangiomas is often disappointing because the swift-flowing blood carries the solution away and disperses it before the endothelium is injured sufficiently to cause thrombosis If the needle, by lucky chance, enters the afferent arterial vessel, the end result is fortuitous and dramatically effective

Combined Injection Treatment and Vascular Ligation of Hemangiomas

Racemose or cirsoid hemangiomas and the huge systemic hemangiomas involving an entire extremity require preliminary ligation of vessels to induce some hemostasis before the injection of sclerosing solutions If the arterial component can be isolated and ligated, subsequent treatment is greatly facilitated. For the systemic hemangiomas of an extremity, multiple ligations of the tortuous subcutaneous vessels at different levels is in order, to be followed by sclerosing therapy In order to avoid the disfigurement of numerous scars for exposure of these vessels, a method of deep ligation without skin incisions has been designed (Fig 228)

Radiation Therapy of Hemangiomas

Hemangiomas are more sensitive to irradiation during infancy and early childhood than in later years, but so are the normal tissues, especially bone, where in close proximity The principle of therapy is to obliterate the tumor by sclerosing fibrosis of the tumor The predictable success of radiation therapy is not sufficient indication for the use of this modality The immediately good after-result is sometimes spoiled by atrophy of the skin and subcutaneous tissues 10 to 15 years later Radiation



FIG. 227 Treatment of hemangioma of hand by cryotherapy and sclerosing solutions. (*Left upper and lower*) A 3-month-old female with a congenital diffuse hemangioma involving the right hand, wrist, and proximal phalanges. The thenar eminence was incorporated by the tumor During 4 months the patient received applications of carbon dioxide snow and injections of sodium morrhuate. The hemangioma was completely obliterated. (*Right*) Appearance of hand 3 years after treatment.

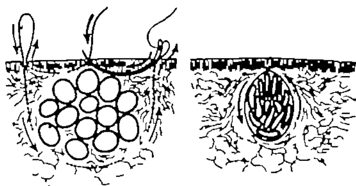


FIG. 228 Technic of subcutaneous ligation of hemangiomas which leaves no external scars except three needle-puncture wounds. Used in conjunction with sclerosing solutions.

telangiectasia developing in the facial skin of children or young adults treated in infancy may require surgical excision and plastic repair The skin overlying the middle of the trunk, i.e., the sternum and vertebral column, has a poor blood supply and radiation treatment results occasionally in late radiation necrosis X ray or radium treatment for hemangiomas of the scalp is too often followed by permanent alopecia

Heavily filtered x ray or radium therapy even in seemingly small doses may interfere with epiphyseal bone growth, and shortening of limbs and facial asymmetries have occurred. Hemangiomas near the breasts of female infants or the external genitals of little girls or boys should be treated by methods other than irradiation, which can seriously retard the natural development of these parts If an infant has an hemangioma near the eye, orbit or eyelid, a preliminary examination by an ophthalmologist is a wise precaution in order to be certain about any defects in the eye related to the tumor and therefore not subsequently attributable to the treatment. The eye cannot be adequately protected if radium is used and radiation cataract or glaucoma secondary to radiation iridocyclitis has been reported many times

To overcome the radiation damage and avoid the late sequelae of transcutaneous x-irradiation of deeply situated subcutaneous hemangiomas, a skin flap has been elevated, exposing the underlying tumor Under aseptic precautions, a sterilized cone attached to a Chaoul tube (transmission anode) is applied at short distance (2 cm.) and with a light filter (0 2 mm Cu) to deliver x-ray of long wave length and feeble penetrating power (50 kv) for a single massive dose (2000–3000 r), after which the reflected skin flap is sutured over the wound The previously reflected skin obviously does not participate in the radiation reaction and in future years shows no cosmetic blemish.

The deeply situated angiomatous masses can be interstitially irradiated by the intratumoral deposition of gold radon seeds (4 mm long, filter, 0 3 mm Au, radon 1–1 5 mc) introduced with special hollow trocar needles In order to avoid unnecessary hemorrhage, the needles are inserted through the normal adjacent skin and thence deeply into the tumor, rather than directly into the tumor Interstitial irradiation of cavernous hemangiomas of the tongue has been successful in our hands There is no other possible means of treatment short of partial or total glossectomy

In the average case, surface applications of radium seldom exceed one to two skin erythema doses, repetition of the dose may be required within 4 to 10 months The skin surrounding the hemangioma is protected by a lead shield perforated to expose the tumor Whenever radium plaques are used at the conventional 1 cm radium–skin distance, the dose varies from 25 to 50 mgh or mc -hrs Contact x-ray therapy may be substituted

The radon bulb (glass sphere, 4 mm diameter) containing 200 to 600 mc and emitting predominantly beta rays is a most useful contact applicator for tiny punctate hemangiomas

Surgical Treatment of Hemangiomas

Many hemangiomas of the skin and subcutaneous tissues are so well encapsulated and redundant that surgical excision and plastic closure is the quickest and simplest method of treatment The fine linear scar is less conspicuous than the flat white skin following the various more conservative procedures The exposure and double ligature of the entering vessels is easily accomplished by traction on the tumor after the circumferential incision has been made, a step that makes the minor operation relatively bloodless

END RESULTS

The end results following the treatment of hemangiomas are usually excellent Their effective control frequently requires prolonged periods of treatment, and controlled patience must be exercised by the physician, the patient, and his family The judicious, unhurried use of one or a combination of treatment methods herein outlined will most frequently be rewarded by a kind, complete cure

CASE REPORT NO. 26· CONGENITAL HEMANGIOMATOSIS CONTAINING INTRATUMORAL BLOOD ISLANDS

H P, a 5-week-old baby, was admitted to the hospital This child, the second infant of the family, was born at term, but was definitely immature in development, being underweight and ill-developed There was a loss of subcutaneous fat and all the superficial veins were markedly distended At birth it was noted that multiple tumors were present over the extremities, chest, back, and abdominal wall, and subcutaneously in the region of the head The liver was quite large and extended 3 fingerbreadths below the costal margin A huge mass occupied the left abdomen and was judged to be the spleen because of its location and notching The other sibling was

a normal infant. The present child bled readily and profusely at the slightest trauma. Some of the subcutaneous tumors of the head were of very large size, particularly in the right temple. The hemangiomas of the right hand and left foot fungated through the skin and bled profusely The other tumors were intracutaneous and subcutaneous and were compressible The child had never been grossly jaundiced, and there was no evidence of ascites

The laboratory studies revealed a platelet count of 68 000 thrombocytes, a reticulocyte count of 2 6 per cent, a hypoproteinemia as evidenced by serum protein level of 4.8 mg per cent, a normal bilirubin and normal prothrombin level. The parents were blood typed for the Rh factor as we considered that the child might have erythroblastosis. The fact that the mother was Rh positive and that the child did not show any jaundice, ascites, or erythroblastic anemia ruled out this possibility One of the tumors of the foot was removed. Under the microscope it proved to be an hemangioma, the site of interstitial erythropoiesis (blood island of Pander) There were numerous normoblasts in the circulating blood and megakaryocytes were present. The diagnosis was hemangioma with erythroblastosis.

X ray films of the skeleton revealed circular areas of bone destruction varying in size from 1 to 3 cm. involving most of the bones of the extremities. Regions of bone destruction were also present in the bony pelvis and skull.

The child improved temporarily after blood transfusions, but would not eat, presumably because of the huge abdominal masses. The eyegrounds were entirely normal There was some suspicion of intracranial hemorrhage. The child died a few weeks later but no postmortem examination was obtained.

Comment

The case was one of congenital hemangiomatosis more than 50 discrete superficial hemangiomas being present. Very likely they were associated with visceral hemangiomatosis and with blood island formation and erythropoiesis developing in the hemangiomas as proved on microscopic study

CASE REPORT NO 27: HEMANGIOMA OF FOREARM THROMBOCYTOPENIC PURPURA SPLENECTOMY SPONTANEOUS CURE

R H., a 9-month-old boy was brought to the clinic because of frightening growth of a tumor of the right forearm When the child returned from the hospital after birth, the mother noticed a quarter sized, slightly elevated, firm, ecchymotic, discolored mass on the volar surface of the upper forearm By the age of 1 month however the swelling and discoloration had apparently disappeared and remained so for 10 to 14 days. The tumefaction then recurred and grew rapidly and progressively

Physical examination revealed a well-nourished infant with numerous ecchymoses scattered over the entire trunk, buttocks, and lower extremities, right arm right lateral chest, and left upper arm. The edge of the spleen was palpable.

There was a large firm tumefaction involving the elbow and upper two-thirds of the right forearm. The elbow was flexed 45 degrees and further motion was markedly limited The hand and fingers were held in flexion. The arm at the tumor level measured 24 cm in circumference There was no increased warmth and no bruit. (Fig 229)

X ray studies of the long bones such as the humerus femora, and right ulna showed elevation of the periosteum with cortical reaction A formal biopsy of the tumor gave the diagnosis of hemangioendothelioma (benign)

The provisional diagnosis was thrombocytopenic purpura of undetermined etiology and hemangioma hypertrophicum

A splenectomy was performed on April 18 1949 The pathologic report of the specimen was not remarkable. There were occasional megakaryocytes in the pulp sinuses and some excess phagocytosis and hematogenous pigmentation. The postoperative course was normal. The platelet count preoperatively varied from 29 000 to 7 400 and postoperatively it rose to a maximum of 17 600 per cubic millimeter of blood. The right arm was placed in a plaster cast because of wrist drop which was believed to be due to pressure by the hemangioma on nerve trunks. On May 11 the patient



FIG 229 (*Left*) Congenital hemangioma of right forearm, intratumoral thrombosis Thrombocytopenia treated by splenectomy (*Right*) Spontaneous cure of hemangioma This illustration was made 11 months after figure at left (Case report No 27)



FIG 230 (*Left*) Spontaneous hemorrhage and thrombosis in hemangioma occurring in an infant with thrombocytopenia (*Right*) Appearance of the cavernous hemangioma 2 years later, showing a decrease in size, the result of spontaneous thrombosis and treatment with sclerosing solutions

was discharged from the hospital with the arm in a postmolded splint

The patient was seen at regular intervals in the clinic On October 7, there was improvement in the wrist drop and the tumor appeared smaller. By March 10, 1950, the child's arm had good freedom of motion He used the arm normally and extended it completely A year later the arm had greatly improved There was still some slight induration in the forearm but the massive tumor had completely disappeared

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SYSTEMIC HEMANGIOMATOSIS

Systemic hemangiomas are those diffuse vascular tumors which usually occupy an entire extremity or portion of the head or trunk. As much as an entire half of the body may be involved in this congenital neoplastic process In a strange paradoxical way this hemangioma may follow the cutaneous pattern of some major nerve, e g., the trigeminal.

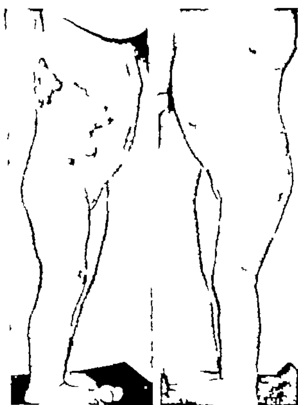


FIG. 231 Systemic hemangiomatosis in a young child. The tumors had been present since birth and had steadily increased in extent

The anlage of this tumor probably begins at the time of limb budding, so that as the arm or leg form, all of the tissues —namely skin muscle, bone, etc.—become infiltrated by the tortuous vessels of the hemangioma The extremity from the shoulder to the nail beds or from the pelvis to the toes may be completely implicated. With this increased blood supply all the tissues of the extremity become hypertrophied and the long bones even increase in length and diameter (It has been shown experimentally that an arteriovenous fistula in animals will result in an overgrowth of

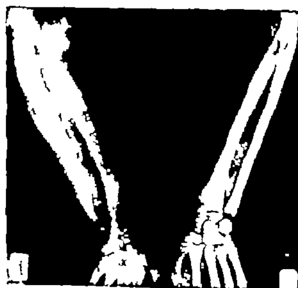


FIG. 232 Systemic hemangiomatosis of the right upper extremity demonstrating overgrowth of the bones of the forearm.

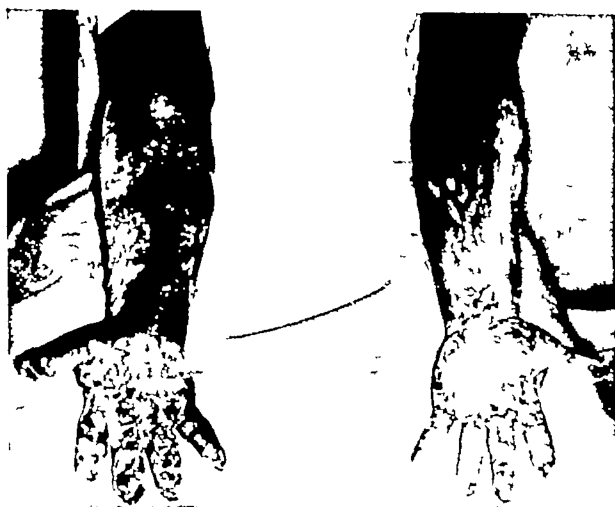


Fig 233 Systemic hemangiomatosis of the right arm and hand Minor starch and iodine test demonstrates vasomotor phenomena associated with hemangiomatosis of the right forearm and hand as compared with normal left upper extremity

bone) The leg or arm is sometimes so heavy, bulky, and cumbersome that the unfortunate patient is functionally handicapped in addition to the disfiguration (See case report No 28)

Fundamentally, the systemic hemangioma is a congenital arteriovenous aneurysmal anomaly There may be multiple communications between arteries and veins. Blood vessels of all types take part in the process, the tumor may be partly capillary and partly cavernous in structure, or it may be a mixed hemolymphangioma Other angiomatous lesions are associated and may be of visceral distribution, for example, in the liver, kidney, or brain

In some infants the systemic hemangioma is perhaps representative of a basic defect in organization and development It is frequently associated with neuro-ectodermal defects of divers types, often identified by curious syndromes and symptom complexes bearing eponyms A description of some of these will be given in detail Imbecility, epileptiform seizures, and neurofibromatosis occasionally accompany the systemic hemangioma in the same patient

It has not been commonly recognized that the systemic hemangioma is constantly associated with hypertonicity of the sympathetic nervous system limited to the extremity involved This abnormal stimulation of the sympathetics is manifested by two phenomena—hyperhidrosis, or pathologic excessive sweating, and vasoconstriction From the center in the hypothalamus, the sympathetic fibers descend through the intermediolateral cell column of the spinal cord, thence through the white rami to the chain of ganglia, and then as gray rami to the peripheral nerves supplying the sweat glands and vasoconstrictor and vasodilator fibers to the blood vessels. The cyanosis of the leg or arm is due in part to delayed venous return and in part to constant arterial vasoconstriction The loss of capillary resistance and the substitution of wider arteriovenous channels result in this effort on the part of the arteries to maintain pressure by vasoconstriction This may be the local cause of the regional sympathicotonia At the time of dissecting these tumors in the operating room, the surgeon is impressed by the rigidity and small caliber of the axillary or femoral artery

The excessive sweating is so great as to be embarrassing and is of course independent of the weather and humidity The sock on the ipsilateral foot may need to be changed dozens of times daily and the hand may drip sweat steadily In one patient, the quantity of fluid lost from the arm was so enormous that the blood analysis revealed hyperproteinemia of a degree comparable to that seen with myeloma Some of the smaller hemangiomas demonstrate this sweating phenomenon It can be shown by the use of the Minor test The Minor solution is composed of the following ingredients iodine, 1 5 to 2 gm , castor oil, 10 cc , and absolute alcohol up to 100 cc The skin overlying the extremity or hemangioma is wiped dry, the solution is painted on, and the area is then dusted with powdered starch With the

opposite uninvolved extremity as a control, the starch-iodine reaction of blue-black color in the presence of sweat is most vivid.

The extent of the arteriovenous shunt in the systemic hemangiomas varies greatly depending on the size and number of the fistulous communications In two or three of our most advanced cases the lesion was predominantly an arteriovenous aneurysm It may become progressively more severe as the child matures There are several clinical and laboratory tests which can be employed to determine this arterial connection e g (1) oxygen saturation tests show a higher concentration in venous blood from the hemangioma than in blood drawn from other veins (2) the swollen extremity engorged with blood can be compressed, but the veins fill more quickly on release than do ordinary varicose veins, because they are arterial varices (3) the visible distended veins do not collapse in the conventional manner on elevation of the limb (4) arteriograms show the immediate dissipation of the opaque substance into the dilated vein, (5) the circulation time in the hemangiomatous limb is measurably slower than in the normal leg or arm (6) in extensive cases, the total blood volume is increased, (7) in the presence of a large arteriovenous fistula, the application of a tourniquet on the limb proximal to the fistula results in a small heart measurement in the teleroentgenogram, an elevation of the blood pressure, and a lowering of the pulse rate.

TREATMENT

Treatment of the systemic hemangioma is difficult and unsatisfactory due to the pervasion of all tissues by the angiomatous process Some may be treated with gratifying results by the combined use of cryotherapy and injection of sclerosing solutions. (See case report No 30) One principle of cryotherapy is to use a very large block of carbon dioxide ice and apply it under pressure, covering a great deal of the hemangioma, the arm or the leg The area is then lubricated with one of the antibiotic jellies or ointments, such as bacitracin ointment or sulfathiazole ointment and then a very tight and strong pressure dressing is applied over the entire extremity occluding the area of treatment, and the hemangiomas are kept compressed. Doing this enables the thrombosis apparently to be more effective than when the blood continues to circulate. The pressure must be diffuse and extended over the entire arm The dressing is not changed for 8 to 10 days after such a treatment.

Surgical dissection of the main artery to the limb in serial operations from the trunk downward and disconnection of venous communications is the best direct attack. If the exact location of the fistula can be determined the operation is greatly simplified. Subcutaneous ligation of the distended veins and the injection of sclerosing solutions will cause some regression of the superficial tumors, but fails in patients with the deep arterial communications A modified Kondoléon operation has been done by us on several occasions in order to make a leg or arm useful. It is usually done in stages under tourniquet control, but even here the blood loss is disproportionately great. Amputation is seldom indicated, but it has been done when gangrene has supervened. Stellate ganglion block will temporarily stop the excessive sweating of arm and hand and overcome the vasoconstriction so that the upper extremity is warmer but in our experience it has not relieved the attendant pain or discomfort.

The following case reports will outline the diverse clinical courses manifested by this unique growth anomaly systemic hemangiomatosis



FIG 234 Arteriovenous fistula *A, B, C, D* Massive arteriovenous fistula treated by ligation of subclavian artery and disarticulation Progressive development since childhood, because the condition was confused elsewhere with simple systemic hemangiomatosis (Case report No 28)

CASE REPORT NO 28 CIRSOID, ANEURYSMAL, SYSTEMIC HEMANGIOMATOSIS OF THE RIGHT UPPER EXTREMITY (ARTERIOVENOUS FISTULA)

W F , a 35-year-old man, was first seen by one of us (G T P) on December 18, 1942 In childhood the right arm had become swollen, beginning with the hand and wrist and extending up to the shoulder At the age of 8 to 10 years the arm was of mammoth dimensions and nonfunctional At the age of 25 an amputation of the arm superior to the elbow was done at another hospital The specimen submitted at that time to Dr Fred W Stewart led to the following microscopic diagnosis "The large nerves have their individual fibers separated by edema There is a definite proliferation of the endoneurial structure outside of the Schwann nuclei Individual axis cylinders are enlarged Intraneural vasa nervorum are enlarged and unusually numerous Numerous blood vessels throughout the section are telangiectatic and cavernous, with thin walls distended by blood and crystalline products of blood decomposition Other vessels are small and proliferating with relatively thick walls lying in a mucinous stroma These vessels have definite embryonal characters The presumptive diagnosis is muscle angioma "

The condition progressed and was treated by other physicians who employed x-ray therapy to control the continued growth of the tumor When first seen in December, 1942, the amputation stump was enormous, with ulceration at the tip and a profuse constant discharge of plasma The lividity and enormous vascular dilata-

tion extended over the scapular deltoid and pectoral regions to produce a pseudo-gynecomastia of the right breast The violet discoloration of the skin extended directly to the midline of the sternum and the vertebral column posteriorly The mass was compressible and huge vascular channels could be felt around the shoulder girdle. The patient's heart was markedly enlarged, with enormous left ventricular dilatation and hypertrophy

Our diagnosis was congenital systemic hemangiomatosis with the arteriovenous fistulous communication developing in fetal life when the right anterior limb bud began to form Hence the hemangioma involved not just the skin and subcutaneous *tissues but the muscles and bones as well.* The earliest roentgenograms showed very marked overgrowth of bone with thickening of the cortex and involvement of the medullary cavity Later roentgenograms of bone showed the destructive process involving not only the remnant of the humerus but also the scapula in the region of the glenoid fossa There were numerous deposits of calcium throughout the tumor characteristic of the phenomena encountered with arteriovenous aneurysms.

The blood volume was *tremendously increased* because of the great venous blood channels utilized by the arteriovenous fistula The venous blood in the right arm, as determined on chemical study was well oxygenated. Venograms showed marked dilatation of the venous system of the right arm The heart was found to be quite large and did not diminish in size on application of a tourniquet to the right shoulder presumably because hypertrophy had occurred instead of dilatation As was to be expected, the venous pressure was markedly increased in the right or involved arm. After the application of a tourniquet to the right shoulder the blood pressure in the left arm increased and the pulse rate became slower These findings together with the clinical appearance, the history and the demonstra*tion of calcium in the tissues confirmed the* clinical diagnosis of arteriovenous or aneurysmal angiomatosis.

Treatment

Because the collateral circulation and venous dilatation involved the entire right thorax to the midline of the sternum and from the clavicle downward anteriorly and posteriorly the only means of approach was through the right supraclavicular space An incision was made parallel to the clavicle and the common carotid artery was fol

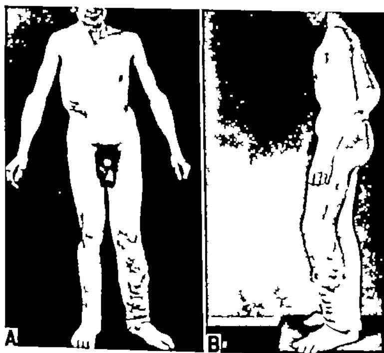


FIG. 235 *A, B* Systemic hemangiomatosis with hemihypertrophy There was overgrowth of long bones, kyphosis, and other osseous abnormalities. (Case report No 29)

lowed into the mediastinum, where the subclavian artery was identified and ligated In the course of this dissection the right subclavian vein was seen as it arched above the level of the clavicle It was huge, with a very thin wall, and was pulsating vigorously

Ligation of the subclavian artery was done proximal to the fistula and the pulsations in the subclavian vein stopped abruptly afterward The operation was completed by an amputation of the right upper arm The resulting wound following this guillotine operation was closed by multiple pinch grafts The patient was given 2500 cc of blood during the operation



FIG 236 *A* Hemangioma unius lateralis treated by cryotherapy and injection of sclerosing solution *B* Five years after treatment, excellent result (Case report No 30)

Comment

This man's plasma protein was very high prior to the operation The convalescence was uneventful and he has been in excellent health and able to work since

CASE REPORT NO. 29
HEMANGIOMATOSIS

J M , a 33-year-old male moron, at birth had a red systemic hemangioma involving chiefly the left lower extremity and trunk, with an associated disproportionate lengthening of the left leg The condition remained relatively stationary until 1937, two years prior to study, at which time numerous new foci appeared in and under the skin of the trunk, neck, and face The hemangioma involved the lower extremity, and became larger in circumference. The swelling was more noticeable on standing

On examination, the patient was found to be a moron, with a small asymmetrical head and marked scoliosis An extensive systemic hemangioma involved the entire lower extremity, with surface discoloration and deep venous sinusoids of large size The left leg was 2 cm longer than the right In the standing position, the left calf measured 40 cm in circumference and the left knee 34 5 cm in circumference, with the leg elevated at right angles, the left calf measured 33 cm and the left knee 30 cm in circumference The angiomatosis extended across the buttocks posteriorly to the anterior surface of the right thigh and abdomen The patient, moreover, had a definite right scoliosis and facial asymmetry, the right side being hemiatrophic (Fig. 235)

The right conjunctiva was pigmented, a pigmented nevus was present above the right upper eyelid, and there was a persistent remnant of the right hyaloid artery

Radiographic studies of the skeleton revealed changes in the bone characteristic of overgrowth associated with angiomatosis The roentgenograms of the left lower extremity notably revealed bones which were larger, longer, and wider than those of the contralateral leg

Treatment was confined almost entirely to the cumbrous left lower extremity which was the major cause of his disability On

numerous occasions subcutaneous ligations of the huge vascular channels were done followed by distal injections of sclerosing solutions such as sodium morrhuate. Considerable improvement has been obtained, but the angiomatosis permeates too much of the extremity including the bone, to permit a dramatic cure by methods so conservative.

CASE REPORT NO 30: HEMANGIOMA UNIUS LATERALIS TREATED BY CRYOTHERAPY AND INJECTION OF SCLEROSING SOLUTIONS

K. K a 7 week-old boy had a congenital diffuse hemangioma involving the skin and *subcutaneous tissues of the entire left upper* extremity extending from the scapula to and including the fingers Radiographs of the upper extremity revealed no abnormalities of the bones Treatment at intervals over a *period of 3 years employing repeated topi*cal applications of carbon dioxide ice and intravascular injections of 5 per cent sodium morrhuate resulted in complete obliteration of the tumor During this interval the infant patient s severe anemia was combated by multiple small blood transfusions Complete clinical regression of the tumor oc*curred, with preservation of good function*

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HEREDITARY HEMORRHAGIC TELANGIECTASIS (RENDU-OSLER WEBER'S DISEASE)

Armand J Quick has defined this symptom complex as follows "Hereditary hemorrhagic telangiectasia is an inherited maldevelopment of the minute blood vessels in localized areas predisposing them to injury and serious bleeding" The requisite triad fulfilling the definition of this disease are (1) mucosal hemorrhages, usually epistaxis (2) familial occurrence, and (3) the presence of telangiectatic small angiomas of skin and mucosa, commonly in the oral and nasal cavities.

The disease is transmitted as a simple dominant affecting both sexes and transmitted either through male or female, with atavistic skipping of individuals or generations as Fitz Hugh has shown. Although the anlagen of the *angiomas* may be congenital, the minute tumors appear relatively late in the development of the individual. The onset of the disease may be heralded in children by nosebleeds but the severe hemorrhages and clinically evident telangiectases start usually in the fourth or fifth decade of life. In some women these tiny vascular *tumors involving* mucous membranes are the cause of vicarious menstruation, *i.e.*, the tumors bleed coincidentally with the menses

Quick has found the source of the common epistaxis to be in Kiesselbach s vascular plexus situated in the lower *anterior segment of the* nasal septum. Although the hemorrhages have been known to occur from the upper respiratory passages, the gastrointestinal tract, and even the kidney (hematuria) epistaxis is the most frequent expression

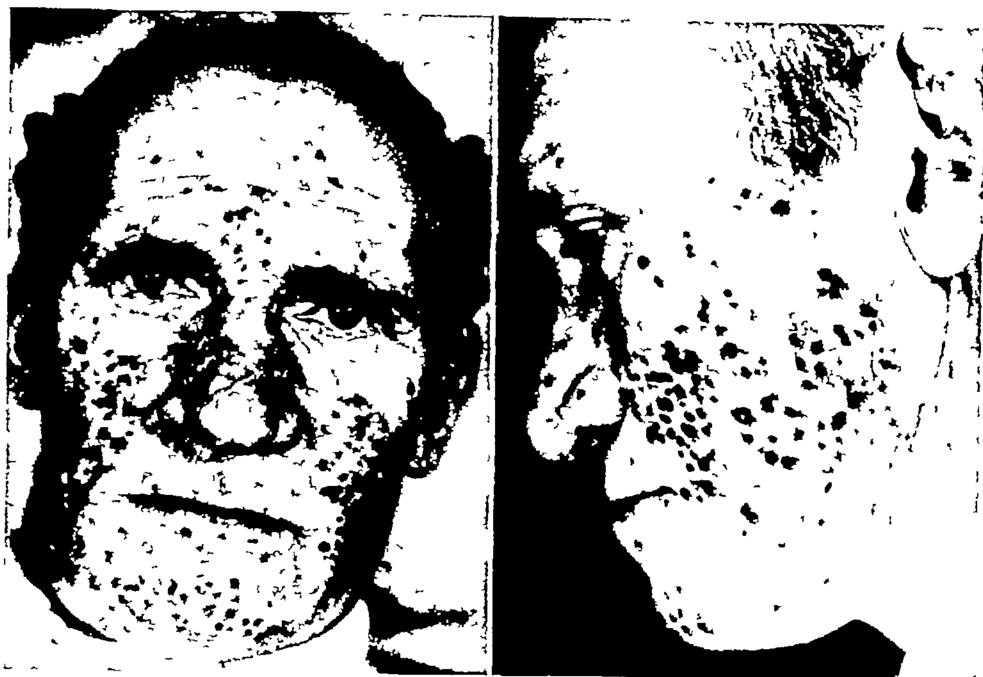


Fig 237 Rendu-Osler-Weber's syndrome Hereditary hemorrhagic telangiectasis (*Courtesy*, Dr Hyman I Goldstein)

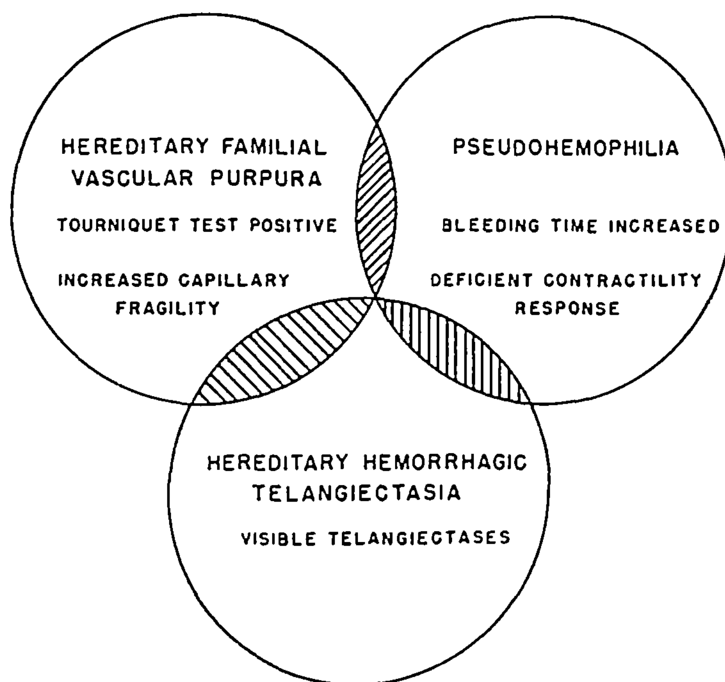


Fig 238 Illustrating certain features exhibited in common by three diseases characterized by abnormal bleeding tendencies (*Courtesy*, Dr Armand Quick)

and can follow simple sneezing One of our patients had recurrent, almost intractable bleeding from the vermilion border of the lips The intermittency and the severity of the bleeding may require repeated blood transfusions It is a serious and crippling disease and is never relieved by spontaneous remission or cure

The differential diagnosis between Rendu-Osler-Weber's disease and hemophilia, pseudohemophilia, and thrombocytopenic purpura is well shown in Table 53 by Quick Emphasis should be placed on the normal coagulating mechanism of the blood Hyman I Goldstein, who has contributed much to our knowledge of this disease, has described a splenomegaly appearing late in the course of the very severe cases

TABLE 53 DIFFERENTIAL DIAGNOSIS OF HEMORRHAGIC DISEASES*

Factors	*Hemophilia*	*Pseudohemophilia*	*Thrombocytopenic Purpura*	*Hereditary Telangiectasia*
Heredity	Recessive sex linked	Dominant sex linked (?)		Simple dominant
Sex involved	Male	Male and female		Male and female
Transmission through	Female	Male and female		Male and female
Bleeding				
Time after injury	Usually delayed	Immediate	Immediate	Immediate
Petechial	Absent	Uncommon	Common	Absent
Ecchymotic	Present	Common	Very common	Uncommon
Mucosal	Uncommon	Severe	Severe	Usually severe
Wound	Severe	Severe	Severe	Absent except at lesion
Hemarthrosis	Common	Uncommon	Absent	Absent
Coagulation time	Prolonged	Normal	Normal	Normal
Bleeding time	Normal	Prolonged	Prolonged	Normal
Platelet count	Normal	Often increased	Decreased	Normal
Tourniquet test	Negative	May be positive or negative	Positive	Negative
Clot retraction	Normal	Usually normal	Absent	Normal

* From A. J Quick *Hereditary Hemorrhagic Diathesis, Pseudohemophilia and Telangiectasis* Springfield, Ill., Charles C Thomas, Publisher 1943 p. 167

The angiomas are usually tiny telangiectatic, reddish or purplish dots, seldom larger than 3 mm. in diameter They are punctate, round, macular sessile, or to use Osler s term, spiderlike.

TREATMENT

Cauterization by acids and heat has not been notably successful. The accessible *hemangiomas* have been obliterated by electrodesiccation employing the monopolar Oudin current. We have found a satisfactory treatment to be contact application of an unfiltered radon bulb in doses of 400 to 600 mc. min. this radon applicator emits beta rays which have such feeble penetrating power as to be absorbed almost entirely in the substance of the angioma. The radioactive-strontium beta-emitter is also a satisfactory method of irradiating these lesions The patient should be taught that firm pressure is the best first aid or immediate treatment. Transfusions and the administration of iron to combat the hypochromic anemia are necessary in the severe cases George Escher has used estrogenic hormones for treatment. He had noted that at the time of the menses and the menopause, when the estrogenic levels were low the patient tended to bleed from her telangiectasis The amount of estrogen used was relatively small, but the results were effective. There is no value in the use of it in the male.

CASE REPORT NO 31, RENDU OSLER WEBER S DISEASE

I H., a 50-year-old Russian Jewish housewife para III had been aware for 15 years of the presence of numerous small red nodules on her tongue. For 2 years she had had intermittent severe nasal hemorrhages. The past history revealed that her mother suffered from frequent nosebleeds and one daughter had numerous episodes of epistaxis On the surface of the tongue were

numerous small, discoid, red, angiomatous nodules Similar lesions were found on the epiglottis, lateral pharyngeal wall, labial mucosa, and nasal mucosa, particularly on the left side of the nasal septum Similar small, red hemangiomatous nodules were observed on the skin of the face, the neck, the palms of the hands, and particularly on the tips of the fingers.

During the succeeding 8 years the patient was under constant medical and surgical care and was admitted to the hospital at least 12 times because of profound hemorrhages occurring from the nasal cavity, mouth, and lips The hemorrhages required nasal packing, surgical excision of bleeding angiomatous nodules, contact radium therapy with a radon bulb, intracavitary radium therapy and gold radon tubes within the nose, low-voltage x-ray therapy, and innumerable blood transfusions The blood count varied usually from 2 5 to 3 0 million erythrocytes After her final examination she bled to death from a hemorrhage originating in the nasopharynx

CASE REPORT NO 32 RENDU-OSLER-WEBER'S DISEASE

S M, a 60-year-old multipara, complained of recurrent hemorrhages from her lips Of occasional occurrence in past years, they had become progressively more severe during the past 12 months They were difficult to control The family tree was difficult to trace because the patient recently immigrated from Europe Two daughters and one granddaughter suffered from epistaxis, the most frequent expression of the disease Involving the vermilion border of the lower lip and extending beyond the right oral commissure were a series of punctate hemangiomas A telangiectatic spot was also seen within the nasal cavity The blood platelet count was 250,000 per cubic millimeter of blood and the prothrombin time was normal The angiomas were obliterated by electrodesiccation

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CONGENITAL NEUROCUTANEOUS SYNDROMES ASSOCIATED WITH ANGIOMATOSIS

Certain neuroectodermal defects involving the central nervous system and peripheral nerves are also frequently found in association with hemangiomatous lesions, which may be intracranial, dermal, and visceral in distribution It is possible for patients with these defects to be intelligent, but in the average case the brain lesion is so gross and so often associated with hemorrhages and structural maldevelopment that variable degrees of mental and psychic impairment occur. In 1928, Harvey Cushing and Percival Bailey made a clinicopathologic study of the intracranial hemangioblastomas They reported that the middle cerebral artery was more likely to be involved by hemangiomatous lesions, due to the wide distribution of its cerebral vessels, therefore, the paracentral convolutions were assumed to be most commonly implicated

Both neuroectodermal mesenchyme and mesodermal angioblastic tissues participate in these diseases, so that one finds glial reactions in the brain, tuberous sclerosis of glial elements, peripheral schwannomas, etc, intimately incorpo-

rated with angiomas of divers types in the same patient. Both histogenetic elements develop simultaneously to produce a lesion accepted as tumor and in some sites constituting an angioglioma.

In classifying these complex entities, Yakovlev and Guthrie have emphasized the tendency for the angiomas to have a neuromeric distribution. Cobb reported the case of a patient with an angioma of the spinal cord causing a compression syndrome with paraplegia and associated with four capillary angiomas (port wine stain type) corresponding to the neuromere of the spinal cord which was affected by the angioma. Levy also reported cases of the neurocutaneous angiomas in which the vascular tumors of certain dermatomeres of the skin were combined with angiomatosis of the respective neuromeres of the central nervous system. In the neuro-ocular vascular syndrome of Lindau von Hippel, the malformation involves the metencephaloretinal components of the neural tube. In the neurocutaneous vascular syndrome of Stürge-Weber and others, the orientation is telencephalo-trigeminal.

The following four congenital neurocutaneous syndromes associated with angiomatosis will be briefly discussed (1) von Recklinghausen's neurofibromatosis and angiomas of the skin (2) Bourneville's syndrome with tuberous sclerosis Pringle's disease, and regional angiomas (3) Stürge-Weber's disease, encephalofacial angiomatosis and (4) Lindau von Hippel's disease, hemangiomatosis of retina and cerebellum.

VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS AND ANGIOMAS OF THE SKIN

Neurofibromatosis is not only associated or coexists with multiple lipomas but also with angiomatous lesions of the skin and mucous membranes Diffuse port wine stains (nevus flammeus) capillary hemangiomas, and, rarely systemic angiomas (*hemangioma unius lateralis*) are found in patients bearing the classic stigmas of von Recklinghausen's disease of peripheral nerves We have frequently encountered this relationship and have been surprised to learn that the association is not commonly known. The neurocutaneous manifestations of neurofibromatosis are accepted as ectodermal malformations but mesodermal tissues undergo hyperplasia or neoplasia *pari passu* with the neurogenic elements, e.g the growth of fibroblasts in the tumors of peripheral nerves (from ectodermal mesenchyme) and the hyperplasia of blood vessels in the central nervous system and skin even to the extent of forming true hemangiomas

The anemic nevus of Vörner also occurs in the skin of patients with neurofibromatosis This lesion has a pale-white color and is quickly obliterated by pressure with a glass slide It appears more distinct and more sharply demarcated if the normal adjacent skin is scratched or irritated sufficiently to evoke a vasomotor reaction. Sebastiani attributes the lesion and its circulatory phenomena to a congenital anomaly of the vasomotor nerves causing vascular spasm. (See Chap 23 for a complete discussion of von Recklinghausen's disease)

BOURNEVILLE'S SYNDROME WITH TUBEROUS SCLEROSIS PRINGLE'S DISEASE AND REGIONAL ANGIOMAS

Of the various neuroectodermal syndromes Bourneville's disease is most constant in its manifestations The fundamental lesion of tuberous sclerosis was described by Bourneville and Brissaud in 1880 Sherlock in 1911 coined the neologism *epiloia* by which name the disease is still sometimes called. Tuberous sclerosis is characterized by nodules in the brain consisting of primitive gliosis or abnormal proliferation of the undifferentiated glia cells or spongio-



FIG 239 A child with Bourneville's syndrome, illustrating the typical butterfly distribution of Pringle's disease (nevus multiplex)

blasts Wielschowski observed the close resemblance of the glial proliferations to similar lesions of the central nervous system found in von Recklinghausen's disease The nerve cells later disappear in the center of the sclerotic nodules There is an hereditary or familial pattern, but it is inconstant

Yakovlev and Guthrie have adumbrated the various signs, symptoms, and lesions comprising this complex disease.

1 Mental defects The great majority of patients are idiots or imbeciles Epileptic seizures are common and may be indistinguishable from the fits of idiopathic epilepsy

2 Nevus multiplex of Pringle Scattered in a butterfly distribution over the skin of the nose, nasolabial folds, cheeks, and skin are numerous nodules, pink, yellow, brown, and red, varying from 1 mm to 1 cm in size This specific and symmetrical predilection has been explained as due to the distribution of the terminal filaments of the fifth cranial nerve Dermatologic nosography has known them by the term *sebaceous adenoma* or *nevus multiplex of Pringle* (It was described by Pringle in 1891) Jadassohn, however, discovered that these skin lesions were not adenomatous nor were they related to the sebaceous glands, in patients with tuberous sclerosis, the nodules consisted of hyperplastic foci of connective tissue (Schwann cells?) and vascular tissue The nodules, in fact, were angiofibromas and analogous in many ways to von Recklinghausen's neurofibromas

3 Other cutaneous manifestations (1) Pedunculated skin polyps (2) Pigmented nevi, sometimes hairy (3) Vorner's anemic nevus (4) Café-au-lait spots (5) Intracutaneous or subcutaneous fibromatous nodules which may become conglomerate to form large bluish-white thickenings of the skin

4 Other congenital malformations Harelip, spina bifida, microcephaly, polydactyly, etc

5 Angiomatous tumors of kidney The frequent vascular tumors of the kidney may provoke symptoms but sometimes are discovered only at necropsy They are congenital tumors, developing in the cortical substance of the kidney, well encapsulated, benign, and of such a structure that they resemble an adenoma

6 Other hemangiomas These may occur not only in the brain but in the skin of the face and extremities

See case reports Nos 33 and 34 for descriptions and further illustrations of Bourneville's syndrome

ENCEPHALOTRIGEMINAL ANGIOMATOSIS (STÜRGE-WEBER'S DISEASE)

The regional distribution of this angioma to involve the face and brain unilaterally has caused a chain of resultant signs and symptoms, originally described by Sturge in 1879, recognized by Harvey Cushing in 1903, and classified as a symptom-complex by Parkes Weber in 1922 The four distinguishing features of this syndrome, although not constantly

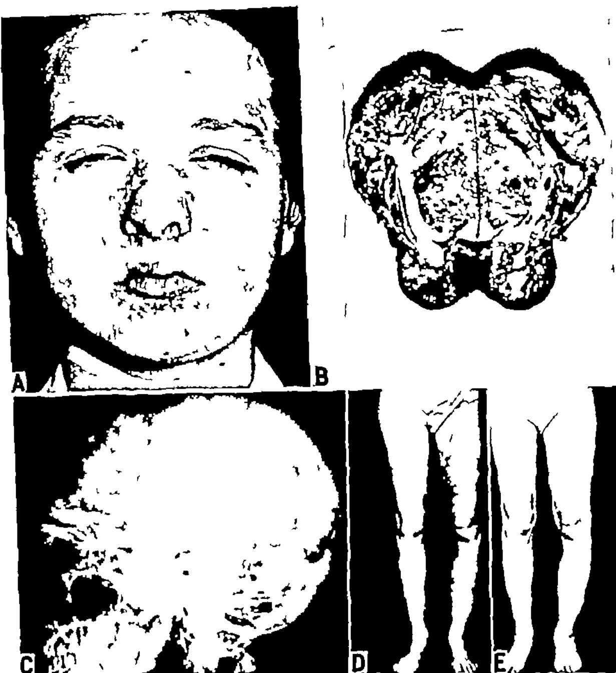


FIG. 240. Bourneville's syndrome. A. Nevus multiplex of Pringle. B Same patient. An encapsulated cortical hemangioendothelioma of the kidney producing hematuria and requiring nephrectomy A frequent association with Bourneville's syndrome. C Same patient. Intracranial calcification associated with tuberous sclerosis. D Infrared photo showing vascularity of hemangiomatous extremity E Same patient. Bone overgrowth associated with the systemic hemangiomatosis. (Case report No. 34)

associated, are as follows the facial distribution of angioma, the central nervous system phenomena, the ocular lesions, and the distinctive roentgenographic findings which are present in 90 per cent of the cases The subject was recently reviewed by Bielawski and Tatelman.

1 The facial angioma. It is a vascular port wine stain limited usually over the distribution of the *trigeminal nerve*, notably in the ophthalmic division. The mucosa as well as the skin is involved. In the case of some of the vascular tumors associated with neuroectodermal defects the distribution of the angiomas in the skin appears to conform with the area of sympathetic innervation rather than with true neuromeres

2. The cerebral manifestations These may be due not solely to the extent of *involvement* by the angioma, but per



FIG 241. Sturge-Weber's syndrome in a 1-year-old infant, illustrating encephalotrigeminal hemangiomatosis

haps in part by hemorrhage within the tumor Generalized convulsions or unilateral epileptiform seizures involving the side opposite the angioma, feeblemindedness, spastic hemiplegia or hemiparesis on the contralateral side of the tumor are expressions of the cerebral damage

3 The ocular disturbances Buphthalmos (infantile glaucoma), unilateral exophthalmos, ocular atrophy, nystagmus, hemianopsia, and ocular palsies may be present individually or as a group

4 Roentgenograms of the skull Bielawski and Tatelman emphasize the importance of intracranial calcification, which is often the type known to be associated with meningeal hemangioma such as sinuous, linear, parallel streaks of calcium deposition, and they also describe a distinctive diffuse calcific density outlining the contours of a part of or the whole cortex of one cerebral hemisphere



FIG 242 Sturge-Weber's syndrome in a patient who suffered contralateral hemiatrophy and encelphalotrigeminal angiomatosis (*Courtesy*, J C Bielawski and M Tatelman, Am J Roentgenol *62* 247, 1949)

HEMANGIOMATOSIS OF THE RETINA AND CEREBELLUM (LINDAU-VON HIPPEL'S DISEASE)

When Lindau was studying cerebellar cysts, he decided that they arose from preexisting hemangiomatous tumors In about 20 per cent of his cases, the cystic hemangiomas of the cerebellum were found in patients who also had angiomatosis of the retina (von Hippel's disease) He also discovered associated pancreatic, hepatic, adrenal, and renal cysts with angiomas in their walls The eponym of *Lindau-von Hippel's disease* has been given to multiple angiomas of the retina and brain It is an hereditary

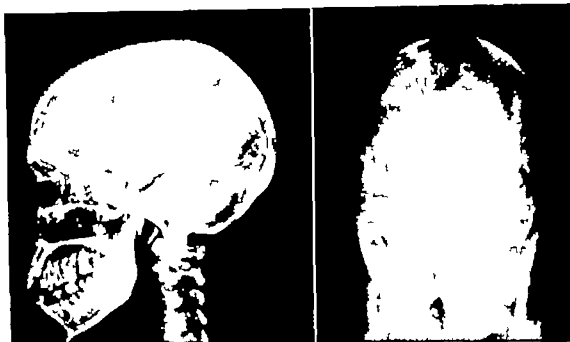


FIG. 243. Sturge-Weber's syndrome. Skull roentgenograms of the patient in Fig. 242, showing hemicranial calcification of cerebral angiomas. (*Courtesy* J C. Bielawski and M Tatelman, Am. J Roentgenol. 62:247 1949)

disease The cysts and hemangiomas most frequently involve the cerebellum, occur less often in the medulla and spinal cord, and are quite rarely if ever observed in the cerebrum. Lindau likened the retinal angiomatosis to a glial reaction.

TREATMENT

The treatment is usually unsatisfactory The external hemangiomas are generally only of minor significance in contrast to the severe disability resulting from intracranial disturbances. The most indicated therapy would be in the neurosurgical realm. One excellent clinical response in a patient with encephalotrigeminal angiomatosis who suffered severe epileptiform seizures was obtained by a subsequent right occipital lobectomy

CASE REPORT NO 33: BOURNEVILLE'S NEUROANGIOMATOUS SYNDROME

F G., a 2 year-old female, at the age of 4 months had mild convulsive seizures occurring two to four times a day for two to three months followed by an equal period free of seizures These epileptiform attacks were not related to meals nor overexertion



FIG. 244. Two-year-old girl with Bourneville's syndrome and cerebral hemangiomatosis. Photograph shows hemangioma of left upper extremity (Case report No 33)

but occurred at any time of the day The child would fall to the floor, flex the head to the left shoulder, flex both legs, and extend them vigorously for several seconds, following which sphincteric control was lost The child was never unconscious but was semiresponsive There was no history of trauma to the head nor of epilepsy in the family

Since the time of birth 9 years ago, the patient's left forearm had been larger than the right forearm, and this discrepancy had persisted and increased to date The angiomatous tumor process involved the left forearm and extended into the left arm and the left shoulder A neurologic consultant found no focal lesions in the brain The skull was apparently normal The plantar reflex was normal He stated that the child was inattentive and not mentally well developed There was a definite enophthalmos of the ipsilateral eye The angiomatous process also involved the left side of the face Roentgenograms of the skull showed a region of intracranial midline calcification 2 cm in diameter in keeping with the diagnosis of Bourneville's tuberous sclerosis At the age of 7 years, the typical lesions in the skin of the face were diagnosed as adenoma sebaceum There was also a recent history of bleeding from the large intestine which may be involved by the tumor process

CASE REPORT NO 34, SYSTEMIC HEMANGIOMATOSIS OF LOWER EXTREMITY ASSOCIATED WITH PERITHELIAL ANGIOMA OF KIDNEY, PRINGLE'S DISEASE (NEVUS MULTIPLEX) AND BOURNEVILLE'S TUBEROUS SCLEROSIS

When this girl patient was 3 years old, her mother observed that the left lower extremity was larger than the right This disparity in size continued until the age of 8 in 1934, when she was first examined in this clinic At that time there was diffuse hemangiomatosis involving the left leg, which was by measurement 2 cm longer than the normal right leg In an effort to equalize the length of the legs by inhibiting bone growth, radiation therapy was administered over the upper and lower tibial epiphyses The enlargement of the leg and thigh was due to diffuse systemic hemangiomatosis involving all the tissues of this extremity

After an interval of six years, *i e*, in 1940 at the age of 14, she experienced hematuria of 13 days' duration A mass was palpable deep in the region of the right kidney Pyelography demonstrated a definite enlargement of the kidney A right nephrectomy was performed for a large tumor, 13 × 10 × 5 cm in diameter, occupying the lower segment of the kidney The pathologist's report was perithelial angioma, benign

Roentgenograms of the skull revealed calcific deposits in the plane of the midparietal region closely adjacent to the lateral ventricle, these were interpreted by the roentgenoligist as consistent with tuberous sclerosis Neurologic consultation was held, and the statement was made that the child was of normal mental development (See Fig 240)

On the face were seen the typical circumoral and butterfly distributions of Pringle's disease, pathognomonic for this neuroectodermatosis

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CONGENITAL OSSEOUS DEFECT ASSOCIATED WITH ANGIOMATOSIS (MAFFUCCI S SYNDROME)

In 1881 Maffucci described the coexistence of multiple hemangiomas and dyschondroplasia as a syndrome which now bears his eponym Maffucci's syndrome differs from Ollier s disease by the additional element of hemangiomatosis The fundamental pathogenesis is a complex mesodermal dysplasia. Apparently the first sign is the appearance of a nodule or nodules on a finger or toe this is followed by other nodules on the hands and feet, arms and legs These nodules grow painlessly and induce deformities which are progressive with the maturation of the body The hands and feet may ultimately become so grotesque and huge as to lose their resemblance to normal structures

The angiomatous element lies in the superjacent soft tissues and skin and is seen in the form of soft, compressible, bluish tumors and dilated veins The growth is uneven or asymmetric, often unilateral in distribution One or more of the long bones may have short shafts The patients are often short and have poorly developed musculature

The disease is found in males two or three times as frequently as in females In quite a number of the early case reports the same statement is repeated, namely that the patients are normal at

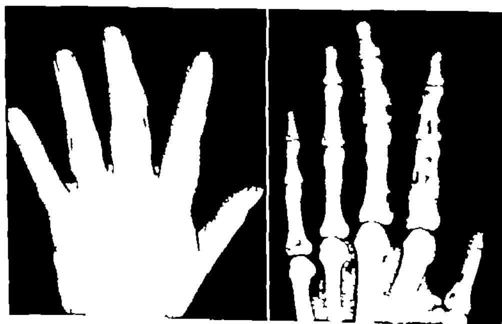


FIG. 245. Hemangiomatosis with dyschondroplasia (Maffucci s syndrome) (*Left*) Defects of the digits with subcutaneous hemangiomas. (*Right*) The typical dyschondroplasia.

birth, and the disease is nonfamilial This assertion is to be doubted, because the very nature of the tumor is such that it should be congenital and one may predict that this concept will later be accepted Certainly, it is demonstrable before the onset of puberty and the neoplasm probably ceases its growth after age 20, *i e*, after full maturity Injuries to the extremities involved by these tumors have not been known to induce the growth of new nodules

Phleboliths are found in the superficial hemangiomas There have been reported instances of associated vitiligo and cerebral glioma The bones involved by the chondromatous masses are susceptible to fractures following trivial traumas and bone union is usually delayed In about 20 per cent of the reported cases, malignant changes (chondrosarcoma) have occurred in the enchondromatous foci

Krause has described the radiographic features as multiple cystic foci (enchondromas) with irregular expansion of the cortex and widening of the shafts, particularly in the hands and feet, but not in the carpal and tarsal bones Similar foci are seen radiographically in the long bones and in the ribs, scapulae, and vertebrae

TREATMENT

The disfiguring hemangiomas may be surgically excised The deformities of the extremities may require orthopedic evaluation and corrective measures. It is not unusual for a digit to be amputated, but in some of the extreme cases the extremity has become so huge and useless as to necessitate a major amputation

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REGIONAL HEMANGIOMAS

Hemangiomas may occur anywhere in the body A few distinctive hemangiomas occurring in locations which present specific problems of treatment will be presented

ORBITAL HEMANGIOMAS

These may involve either the eyelid or conjunctiva, or they may develop in the retrobulbar fat and cause unilateral exophthalmos Although it may be possible to dissect this tumor out by one of the well-known surgical approaches, the operation is often uncertain, bloody, incomplete, and mutilating, especially when the tumor is retrobulbar and extends within the sphenoidal fissure We have obliterated massive tumors of this type by the cautious use of sclerosing agents

HEMANGIOMAS OF THE TONGUE

The lingual hemangiomas are usually cavernous in type and congenital in origin The tip of the tongue is the more common site, but the entire tongue may be involved With arterial communications it may become an erectile organ of enormous dimensions, the macroglossia angiomatosa (See case report No 35) Profuse hemorrhage can follow the slightest trauma from a minor bite or rough food The bulk of the tumor may interfere with mastication and speech Hemangiomas of the tongue which are bleeding and ulcerated and which are not suitable for interstitial irradiation are removed by partial glossectomy preceded, of course, by unilateral or bilateral external carotid artery ligation



Fig. 246 Cavernous hemangioma of the tongue.



Fig. 247 Cavernous hemangioma of the tongue (macroglossia angiomatosa) (Case report No 35.)

Hemangiomas of the Stomach

Gastric angiomas are of great rarity we have been able to collect only 16 reported cases from medical literature. In a series of 25 gastrointestinal angiomas reported by McClure and Ellis in 1930 there was none of gastric origin. Gastric hemangiomas are no doubt congenital, although in this collected series only 5 were detected in patients under 30 years of age. Stockis reported the case of an infant of 12 days dying after severe hematemesis and melena from a gastric angioma. The distribution between the sexes was 9 females and 7 males There was no site of predilection within the stomach. The hemangiomas of the stomach ranged in size from 1.5 to 10 cm in diameter The symptoms and signs produced by these neoplasms and leading to surgical intervention or death were those provoked by other gastric tumors namely (1) dyspeptic complaints (2) mechanical difficulties, and (3) complications, notably hemorrhage and anemia. The incidence of intragastric hemorrhage was naturally high.

In only one case report (Kaijser) was mention made of an association with cutaneous hemangiomas The preoperative diagnosis in 3 patients was cancer in 3 other patients benign tumor in 3 other patients a radiographic filling defect in the stomach without definite diagnosis and in 1 patient, peptic ulcer The gastric hemangiomas were of the sclerosing, capillary and cavernous types. Some form of gastric resection was done in 9 of these 16 patients. Four patients underwent exploratory laparotomy and biopsy 2 of these were successfully treated by irradiation (Kaijser Guisez) Therefore, it may be concluded that the occurrence of a profound anemia in a young patient whose roentgenograms reveal a spherical gastric tumor should suggest the possibility of an hemangioma of the stomach.

Intestinal Hemangiomas

The small intestine and colon are occasionally the sites of multiple hemangiomas, usually associated with known superficial tumors Cryptic intestinal hemorrhages herald the presence of these neoplasms, surgical intervention with resection and anastomosis is occasionally necessary as the repeated hemorrhage may be almost exsanguinating Hemangiomas in the gastrointestinal tract are ignored unless obstruction or hemorrhage necessitates surgical intervention, at which time the accepted technical procedures are followed

Hemangiomas of the Liver

The rare cavernous hemangiomas of the liver are usually discovered on necropsy, although sometimes they provoke symptoms which lead to surgical intervention Preoperative differential diagnosis with other nodular and palpable hepatic enlargements is almost impossible Alarming intraperitoneal hemorrhage may follow an injury to the upper abdomen These cavernomas of the liver may be singular or multiple, as small as a pea or as large as a head They usually lie just beneath, or project from, the surface of the liver They are often, but not always, associated with hemangiomas of other locations Ribbert carried out interstitial injections of the tumor and demonstrated that the material did not pass from the cavernoma to the liver tissue, from which evidence he concluded that the neoplastic vessels showed a definite independence of the normal circulation in the liver Virchow was able to fill these cavernous angiomas of the liver by injections through the portal or hepatic veins or hepatic artery Virchow also believed that hemangiomas of this location sometimes underwent spontaneous disappearance, leaving only a residual scar Hemangiomas of the liver may enlarge rapidly during pregnancy

Hemangiomas of the liver exhibit a certain degree of radiosensitivity The enormous cavernomas can be obliterated by high-voltage x-ray therapy (See case report No 36 for details of the successful irradiation of a liver hemangioma) Cavernous hemangiomas of the liver are sometimes resectable by enucleation as they often are encapsulated We have performed this operation with insignificant blood loss by proceeding with extreme care until the vascular stalk of the tumor was encountered Hepatic lobectomy may be indicated (See case report No 37)



Fig 248 Cavernous hemangioma of the liver, treated successfully by high-voltage roentgen irradiation (Case report No 36)



Fig 249 Hemangioma of the liver occupying a major portion of the right lobe It grew rapidly during pregnancy and was successfully excised after the fifth lunar month of gestation without interruption of pregnancy Photograph at operation showing intact tumor before excision

HEMANGIOMA OF SKELETAL MUSCLE

This variety may occur *de novo* as an isolated tumor in one muscle belly or group of muscles or it may be part of a systemic hemangiomatosis involving an entire extremity In the former case it is difficult to diagnose and to be distinguished from other deeply situated somatic tumors benign or malignant. The following six diagnostic points are perhaps helpful (1) diffuse tumefaction within the muscle proper (2) turgescence or temporary enlargement of the lesion with an extremity pendant or after application of a tourniquet above, (3) decrease in size of the tumor after elevation of arm or leg, (4) pain and functional disability (5) aspiration biopsy secures blood instead of identifiable tumor tissue and (6) the sometime appearance and recognition of calcium deposits or phleboliths within the tumor The patients are generally under 30 years of age. Ewing found the forearm to be the most frequent site and the triceps femoris to be the particular muscle

HEMANGIOMA OF BONE

Although bone is considered to be a rare primary location for such a common neoplasm as hemangioma, it is very likely that many such tumors exist undetected throughout life because the majority are slow growing and asymptomatic. They



FIG. 250. Hemangioma of the liver (*Left*) Preoperative roentgenogram showing displacement of the intestines due to a cavernous hemangioma of the right lobe of the liver (*Right*) Gross specimen of the hemangioma of the liver successfully treated by right hepatic subtotal lobectomy (Case report No. 37)

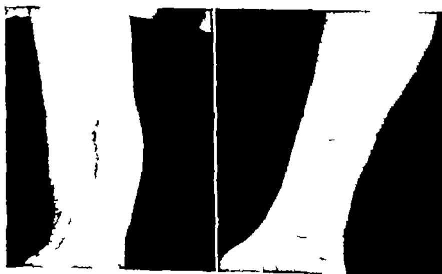


FIG. 251 (*Left*) Recurrent hemangioma located in the depths of the muscles of the forearm and producing an ill-defined bulge. (*Right*) Photograph 3½ years after surgical resection of the muscle hemangioma.

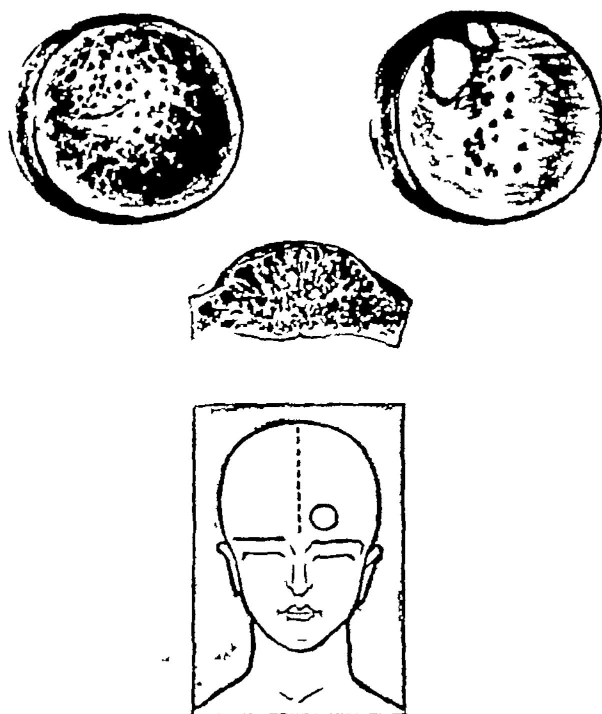


Fig 252 Hemangioma of bone (calvarium) Removed by trephination

may be discovered coincidentally at the time of radiographic examination for other lesions The microscopic appearance is that of a benign hemangioma, usually of the cavernous type, infrequently of the capillary variety The bones of the skull are most frequently involved, but other bones, namely, the vertebral column (especially the lumbar vertebrae), scapula, os innominatum, ribs, and phalanges, may be the sites of origin Bucy and Capp have furnished exact descriptions of the radiographic appearances of primary bone hemangiomas (1) in the vertebral lesions the vertical striations are characteristic and diagnostic, (2) in the flat bones, notably the skull, scapula, and os innominatum, sunburst trabeculations of unusual size radiate usually from a common center and chiefly from the plane of the bone, and (3) in the cylindrical bones the usual loculations of the tumor are small and interspersed with a fine fibrillary framework The cortex is usually destroyed but may extend into the center of the expansive tumor The periosteum may be elevated or expanded but is seldom ruptured The x-ray picture of hemangioma of bone may so closely simulate other bone lesions, such as giant-cell tumor, fibrous dysplasia, or eosinophilic granuloma, that a biopsy may be necessary to establish a correct differential diagnosis Hemangioma of the calvarium often erodes through inner and outer plates, it is difficult to distinguish from dural endothelioma

Cavernous hemangioma of a vertebra may provoke persistent backache and thereby lead to discovery through x-ray examination The inaccessibility of this tumor and its intimate incorporation with an irremovable structure prohibit any attempt at complete surgical re-



Fig 253 (*Left*) Hemangioma of twelfth dorsal vertebra (*Right*) Calcification and healing of hemangioma of the twelfth dorsal vertebra following deep x-ray therapy

moval. X ray therapy has been quite satisfactory in exercising growth restraint and recalcification of the damaged bone. This tumor is moderately radio-resistant, therefore, rather large doses are necessarily administered through small and accurately localized ports. The hemangioma may be so destructive as to permit collapse of the body of the vertebra and give rise to a protruding tumor with compression of the spinal cord. Whenever symptoms of spinal cord compression occur laminectomy is indicated as an emergency operation. X ray therapy at such a time is hazardous because the length of time elapsing before the irradiation becomes effective is so long that the damage to the spinal cord may become irreparable. It should be realized that laminectomy for hemangioma may result in considerable hemorrhage and shock, so the operation is not without danger. Spinal braces or splints are essential prophylactic measures against collapse of the vertebra.

Hemangiomas of the bones of the extremities respond well to deep x ray therapy. Accessible hemangiomas of bone may be suitable for a direct surgical attack. Curettage of the tumors in long bones with implantation of bone chips, rib resection trephine and removal of a plate of calvarium, partial scapulectomy segmental resection and bone grafting are all feasible measures under certain conditions.

Bone Changes Secondary to Hemangiomas of Soft Tissues

Bone changes secondary to hemangiomas in closely adjacent soft tissues follow four common patterns.

1. Local erosion and destruction of bone. The adjacent or proximate hemangioma, by constant pressure and in the case of cirsoid or arterial hemangiomas by pulsating pressure, wears away the bone, leaving an irregular x ray picture showing combined destruction and regeneration.

2. Exostosis or osteoma. Bony outgrowths can develop at sites on the bones overlapped by deep hemangiomas. The similarity of sites of these



Fig. 254. Cavernous hemangioma of leg with associated bone changes (tibial cortex). (*Left*) Shows the subcutaneous hemangioma. (*Right*) Roentgenogram showing the irregular erosion of the underlying tibia. (Case report No. 39.)

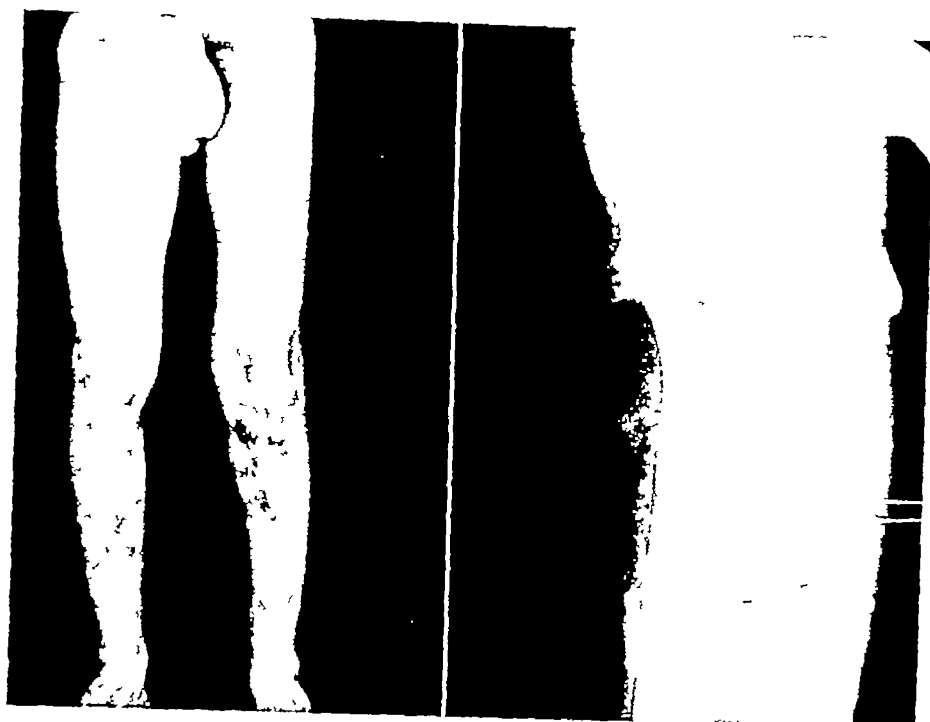


FIG 255 Cavernous hemangioma of leg with associated bone changes (tibial spur) (*Left*) Photograph showing the soft-tissue hemangioma (*Right*) Roentgenogram demonstrating the tibial spur (Case report No 40)



FIG 256 (*Left*) Systemic hemangiomatosis of left upper extremity with associated osseous changes (*Right*) Roentgenogram showing the periosteal and endosteal changes in the ulna and radius

two lesions speaks against coincidental occurrence Whether the increased vascularity of the part causes the abnormality or not remains a moot question

3 Local overgrowth or hypertrophy of the bone The diameter of the bone is locally expanded, thickened, and hypertrophied rather than osteolytic

4 Elongation of long bones of extremity In the presence of a systemic hemangioma or hemangioma unius lateralis, involving an entire extremity, it is not uncommon for the long bones of the affected side to lengthen perceptibly, even enough to cause a limp through disparity in length with the normal side We attribute this phenomenon to the greatly altered circulation to the bone with venous stasis and more direct arteriovenous communications than through the conventional capillary network Support has been lent to this hypothesis by the experiments of Janes and Musgrove at the Mayo Clinic They used five young dogs in each of which an arteriovenous communication was made be-



FIG. 257 Systemic hemangiomatosis of extremity associated with elongation of bones and cavernous hemangioma of colon. (*Left*) Soft tissue hemangiomas are shown invading the left lower extremity (*Right*) Roentgenogram showing the marked elongation of bones of left extremity (Case report No 38)

tween the external iliac artery and vein of the left hind leg and in which actual measurements of the femur and tibia were made 3 to 14½ months after the fistula was established. The right tibia and femur were used as controls From their studies they concluded that the length and circumference of the main bones of an extremity of a dog actually could be increased if a fistula was created before the epiphysis had closed. (See case reports Nos 38, 39 and 40 which illustrate the ways in which osseous changes accompany hemangiomas)

MISCELLANEOUS REGIONAL HEMANGIOMAS

These present specific problems inherent to their sites of origin They are too numerous to discuss here.

CASE REPORT NO 35: HEMANGIOMA OF TONGUE

D S a 50-year-old Syrian male had multiple hemangiomas of the head and neck and a huge hemangioma involving the major portion of the tongue In recent years the tongue had become so bulky that he could close his mouth and swallow only with difficulty and there was considerable interference with his speech On examination a huge cavernous hemangioma was found to occupy the major portion of the tongue and to extend along the lateral aspects deep into the pharynx, where it involved also the left tonsil and left piriform sinus. The mass was compressible. The presumptive diagnosis was cavernous hemangioma of the tongue (macroglossia angiomatosa) (See Fig 247)

In the course of three months, a total of 18 separate injections of 5 per cent sodium morrhuate, from 1 to 2 cc. each were given into the substance of the tongue with progressive thrombosis fibrosis, and regression. The end result was a great improvement

CASE REPORT NO 36: RADIATION THERAPY OF CAVERNOUS HEMANGIOMA OF LIVER

W Z a 55-year-old man had known of the presence of a tumor in the right hypochondrium for the past ten years. His family physician had detected the presence of

this mass, which enlarged slowly and was asymptomatic One month before examination, the patient experienced attacks of syncope followed by anemia and progressive enlargement of the mass in the upper abdomen

On examination of the patient, there was a huge tumor, freely movable, situated in the upper abdomen and apparently originating from the liver An exploratory laparotomy was performed, and a huge cavernous hemangioma involving both lobes of the liver was encountered The tumor occupied the entire upper abdomen A biopsy confirmed the diagnosis of hemangioma The tumor was technically inoperable (Fig 248)

Because of the recent rapid growth of the hemangioma, with intratumoral hemorrhages, and because of the known radiosensitivity of hepatic cavernomas, high-voltage x-ray therapy was given over an enormous field, 16 × 28 cm , employing 250,000 volts, with a 1 5 mm copper filter, 70 cm target-skin distance, 30 ma , 250 r daily for 10 consecutive days or a total dose of 2500 r administered to the entire liver The treatments were completed on December 5, 1942

Ten years later, the liver margin was barely palpable, the liver as a whole was within the limits of normal size No nodularity of the liver margin could be palpated The patient had gained 30 lbs in weight

CASE REPORT NO. 37 SURGICAL RESECTION OF CAVERNOUS HEMANGIOMA OF LIVER

M G , a 61-year-old man, complained of pain in the right upper abdominal quadrant for a period of one and a half years There was coexistent slight indigestion The pain radiated to the back There had been no loss of weight On palpation a deep, rounded mass could be felt in the region of the right hepatic lobe Roentgenograms of the stomach and gallbladder showed these organs to be entirely normal and functioning well In all films, however, a spherical mass in the region of the liver was seen pressing against the pyloric antrum and gallbladder, deforming these organs through extrinsic pressure A presumptive diagnosis of hepatoma was made

At operation on October 3, 1947, a vascular, purplish-red tumor 10 × 7 cm in diameter was found on the undersurface of the right lobe of the liver medial to the ampulla of the gallbladder and pushing the gallbladder toward the right side The tumor was dissected free of the liver until the vascular pedicle was located, it was doubly clamped, severed, and ligated, after which there was no further bleeding in the process of dissection Convalescence was uneventful (Fig 250)

The pathology report was benign cavernous hemangioma or cavernoma of the liver

CASE REPORT NO. 38 BONE CHANGES ASSOCIATED WITH HEMANGIOMA

M B , a 2½-year-old girl, applied for treatment of a huge systemic hemangioma involving the entire left lower extremity, buttock, vulva, and true pelvis This child was constitutionally and mentally inferior, there was definite cretinism Partial excisions were done only because of necessity, due to hemorrhages from the cutaneous part and to infection of the intrapelvic portion with abscess formation The angiomatous tumor incorporated muscles as well as other soft tissues The bones of the left leg were of normal texture but markedly elongated in comparison with the normal right leg, especially as the child grew (See Fig 257)

CASE REPORT NO. 39 BONE CHANGES ASSOCIATED WITH HEMANGIOMA

J J M , a 30-year-old man, applied for treatment of a congenital tumor 6 × 8 cm in size, situated subcutaneously over the middle of the shaft of the left tibia It caused increased pain on walking It was an ovoid, soft, bluish, compressible tumor through the base of which could be felt the irregular contour of the eroded underlying tibia Roentgenograms revealed cortical thickening of the fibula and tibia with areas of osteoporosis and osteosclerosis in the tibia (Fig 254) Intermittent intratumoral

injections of 5 per cent sodium morrhuate followed by Elastoplast compression resulted in complete thrombosis and disappearance of the tumor

CASE REPORT NO 40: BONE CHANGES ASSOCIATED WITH HEMANGIOMA

J R., an 8-year-old boy applied for treatment of a congenital angioma situated below the left knee and overlying the upper end of the tibia Surgical excision was done The case was reopened eleven years later at which time the recurrent angioma was much larger and extended superiorly to the femoral trigone where a thrill could be palpated. A roentgenogram of the leg showed an osteoma (exostotic) on the inner side of the upper end of the shaft of the tibia projecting into the angiomatous lesion (Fig 255) The left lower leg, ankle and foot exhibited the usual phenomenon of profuse diaphoresis and frigidity (vasospasm) due to associated sympathicotonia. Surgical excision and skin grafting were successfully performed.

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THE GLOMUS TUMOR*

The glomus tumor is a small, benign, rare and painful neoplasm of the skin and subcutaneous tissues, occurring usually on the extremities chiefly on the hands and feet and often in the nail bed. The tumor evidently is derived from the glomic end-organ apparatus which is a normal structure of a bizarre arteriovenous anastomotic type with the apparent function of regulating blood flow to the extremities.

HISTORIC REVIEW

For more than a century physicians have correlated the presence of tiny intracutaneous nodules with excruciating, radiating pain. A host of various terms have been proposed the majority of which have been descriptive rather than histogenetic in nomenclature. William Wood in 1812 described these painful, subcutaneous nodules characterizing them as minute, benign tumors of slow growth and long duration, and associated with pain of an acute inter

* In collaboration with Manuel Riveros.

mittent, and spasmodic character. Kolaczek in 1878 described such a tumor occurring subungually in the great toe; he pronounced it to be an angiosarcoma. Chandelux in 1882 reported two instances of subcutaneous, painful tumors, one occurring in the forearm and the other in the arm; his diagnosis was tubular epithelioma of sweat gland origin. Muller in 1901 classified the neoplasm as a perithelioma, based on its vascular structure. Masson in 1919 studied a subungual tumor of this type, noted the resemblance of the lesion to the glomus coccygeum, and first conceived of its structure as a bizarre arteriovenous anastomosis. Masson described the structure of the tumor as comprised of blood vessels, some with muscle walls and others surrounded by the characteristic epithelioid cells. He also recognized the large corpuscles of Pacini, compressed and attached to the capsule of the tumor, which he considered a sufficient explanation for the attendant syndrome of intense pain. In 1920 Barré, a French neurologist, helped to clarify this clinical entity by describing the presence of such a tumor in an 18-year-old girl. It was situated in the terminal phalanx of the right middle finger. Severe pain, as with Horner's syndrome, radiated to the elbow and neck. Simple surgical excision effected a cure with relief of symptoms. In 1922 Barré reported three additional cases.

THE NORMAL GLOMUS

The glomus is a normal end-organ apparatus consisting of an arteriovenous anastomosis functioning without an intermediary capillary bed. The cutaneous glomus was first described by Hoyer in 1877. Sucquet many years ago also described the presence of peculiar blood vessels, particularly in the palms and soles, which were larger than the ordinary capillaries and communicated directly into adjacent veins without the intervention of the customary capillary network.

It is to Pierre Masson and to Nicholas Popoff that we owe most of our present knowledge concerning the normal anatomic structure and function of the glomus. Popoff described the digital glomus as a normal anatomic unit consisting of an afferent artery, Sucquet-Hoyer canal or arteriovenous anastomosis proper, preglomic arterioles nourishing the constituents of the glomus, clear periglomic zone or expansion zone furnished by a neuroreticular mechanism controlling the function of the Sucquet-Hoyer canal, an especially arranged system of collecting veins, and an outer lamellated collagenous zone surrounding the entire glomus. The glomic system occupies a definite zone in the cutis, namely, the stratum reticulare. The afferent artery to the glomus, according to Bailey, originates from branches in the subcutaneous tissues running a course parallel to the skin, and this artery forms from one to four separate Sucquet-Hoyer canals. In the afferent artery are cushionlike endotheliomuscular elevations, the function of which was considered by Popoff to be the direction of blood flow into the canals. These canals are said to be free of elastic tissue, with the exception of the proximal part. They are surrounded with a clear, wide zone of loose, fine collagenous reticulum enclosing a rich network of nonmedullated nerve fibrils. According to Popoff, this neuroreticular mechanism controls the function of the canals. In the muscle layer of the canals are large cells with clear or vacuolar cytoplasm; these are referred to as the epithelioid or glomus cells as they apparently occur only in the cutaneous glomus or in the glomus tumor. According to Bailey these cells are commonly considered to be postembryonal angioblasts, smooth-muscle cells, specialized neuromuscular cells, with intimate connections with the network of nonmyelinated nerve fibrils. The

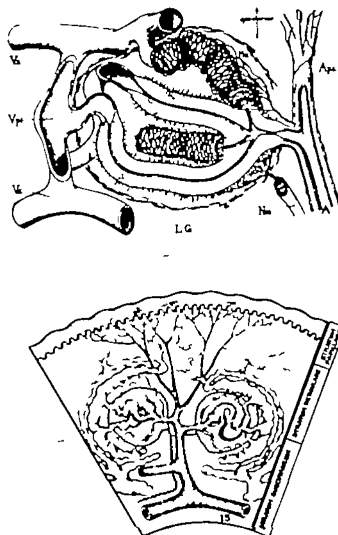


FIG 258. The digital vascular system (Popoff) The normal glomus body (*Courtesy* Dr N W Popoff and A.M.A. Arch. Path. *18*:295 1934)

canals empty into primary collecting veins lacking in musculature but richly supplied with elastic tissues These long and wide collecting veins encircle the glomic unit and form a voluminous receptaculum. Popoff described the entire glomus as surrounded by coarse, lamellated collagenous tissue which separates the glomus from the other structures of the cutis

The function of the glomus has been generally agreed upon by the majority of anatomists and physiologists The normal glomus is thought to control arteriovenous circulation within the fingers and extremities By so doing, it apparently can regulate both the local and the general temperature of the body through the dissipation or conservation of
Experimentally it has been show
Grant that it is the agency of the g
that maintains the temperature c
rabbit's ear when exposed to cold
cyanosis of the nail beds in perso
posed to frigid climate has been
ally observed. Clara has expresse
belief that the glomic structures i
penis are endowed with the funct
regulating the mechanism of penile
tion. Bailey has considered the
bility that the cutaneous glomus
function as a shunt in the mainte
of blood pressure, but, as he state
has not been verified as yet. Wh
glomic system is fully dilated, th
persal of heat is increased beca

the tremendously accelerated flow of blood through the fingers. When the glomic system is closed, heat is conserved by shunting the blood through the capillary networks.

The normal glomus measures from 60 to 220μ. In serial sections of the great toe, Popoff found 18 glomic structures on the ventral surface, 10 on the lateral surface, 24 in the nail bed, and 12 in the nail matrix. They are distributed widely over the body but occur more frequently, of course, on the extremities, particularly in the nail bed and fingertips, then next in frequency on the palmar and solar aspects of the first, second, and third phalanges of the upper and lower extremities. They occasionally appear on the thenar eminences and the heel, less frequently on the penis and urethra. The glomus is apparently absent during intrauterine life. It undergoes atrophy, and the number of glomic units decreases with advancing age. Glomus tumors, of course, occur occasionally in locations where the normal glomic structure is infrequent, but it is possible for an aberrant glomus to occur in almost any situation.

PATHOLOGIC ANATOMY OF THE GLOMUS TUMOR

Various synonyms for the glomus tumor are *angiomyoneuroma, tumeur du glomus neuromyoartériel,* and *glomangioma*. The glomus tumor exhibits considerable variation in structure but, all in all, bears a resemblance to the normal glomus unit.

Masson and Barré independently described the vessels associated with the glomus tumor as of two chief types. In one, the layers of circular smooth muscle were separated from the endothelium by a collagenous membrane. These smooth-muscle cells themselves were surrounded in a circular fashion by larger cells with clear cytoplasm and globular nuclei which blend with the characteristic polygonal epithelioid cells. In the second type of blood vessel, the endothelium was bordered directly by the so-called glomus or epithelioid cells without the interposition of smooth-muscle fibers. Bailey, in a later article in which he described the blood vessels peculiar to the glomus tumor, also noted that they lack elastic laminae, which he

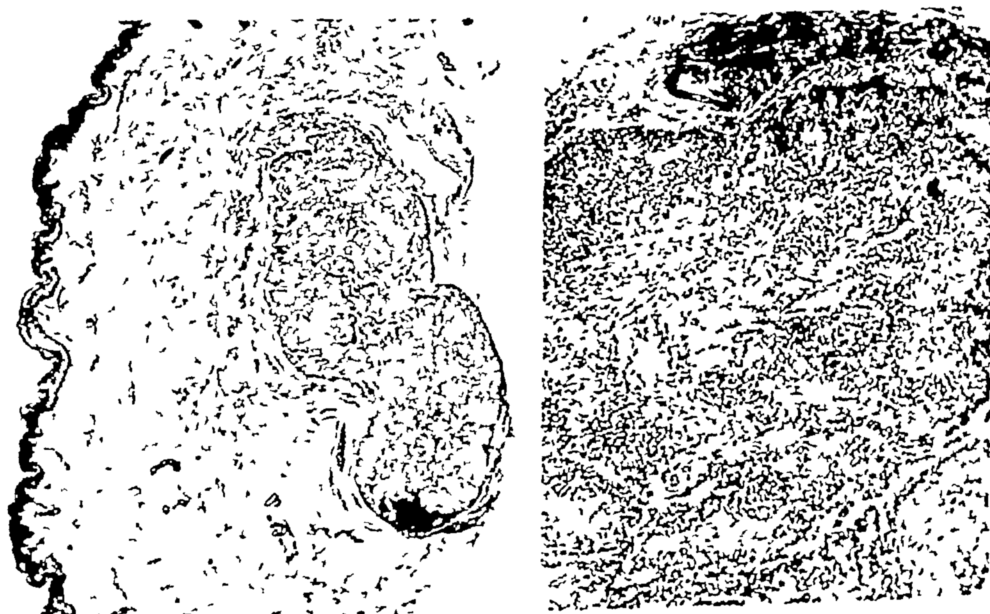


FIG. 259. Glomus tumor. Photomicrographs illustrating the histologic structure of the glomus tumor (glomangioma). (*Left*) Low-power photomicrograph showing the tiny size of certain glomus tumors. (*Right*) Typical glomus tumor presenting epithelioid cells with a variable collagen stroma dispersed throughout. Note the numerous dilated, thin-walled blood vessels.

believed was good evidence that the glomus tumor is derived from the Sucquet Hoyer canals inasmuch as these canals also lack elastic laminae while the preglomic and postglomic venules are provided with elastic laminae

The epithelioid cell is peculiar to the glomus unit and to the glomus tumor According to Bailey they are arranged in three different fashions "A. They may be closely packed together in the walls of blood vessels with single coarse collagen fibers intervening between adjacent cells, or B The cells may be clumped in large masses without vascular lumens or C The epithelioid or glomus cells may be separated from one another by a homogeneous material which takes the same stain as collagen, but lighter than collagen fibers" Bailey prefers the term *glomus cell* and describes the cell as round or polygonal in shape and containing clear cytoplasm without glycogen, fat, or mucin. No myofibrils can be identified.

In some glomus tumors the blood vessels are so large that they resemble true angiomas The epithelioid or glomus cells are supplied usually with nonmyelinated nerve fibers, which run in innumerable fasciculi in the connective-tissue septa between the neighboring blood vessels At the periphery of the neoplasm, the larger nerve trunks are surrounded by schwannian sheaths

The dimensions of the tumors in our personal experience varied from 5 mm to 2 cm In three of our patients the tumor actually involved the bone—in these instances the terminal phalanges on the hand The tumor is fundamentally of benign character case reports of metastasizing glomus tumors remain debatable A malignant tumor of similar origin, or at least one from the perivascular cells of Rouget, is referred to as a *hemangiopericytoma* This tumor is the closest analog of the glomus tumor of all malignant neoplasms

SYMPTOMATOLOGY AND DIAGNOSIS

The glomus tumor is usually single but may be of multicentric origin one of our patients had 3 such tumors In our group of 20 patients there was no significant racial distribution although Stout was of the belief that the tumor is more common in Jews The color of the tumor varies from deep red to purple or blue, with the blue color more predominant. There is a striking and characteristic variation in color with changes in temperature The tumor is sharply de



FIG. 260 Glomus tumor Photomicrographs illustrating samples of structure of glomangiomas (*Left*) A marked hyaline reaction encompasses relatively few epithelioid cells. (*Right*) The epithelioid cells (pericytes) compose most of the section, with a relatively slight stromal reaction. Very few vascular spaces are present

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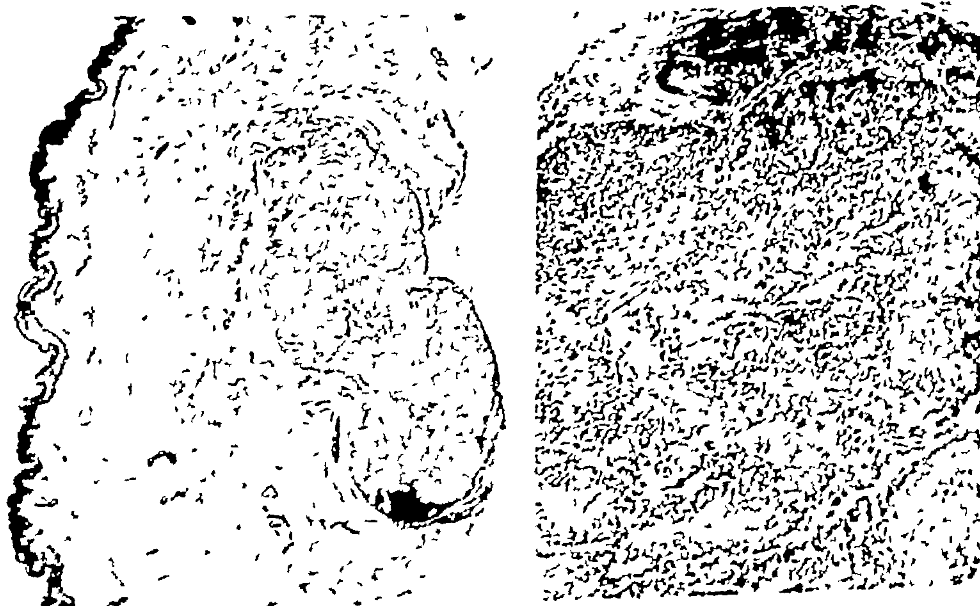


FIG. 259 Glomus tumor Photomicrographs illustrating the histologic structure of the glomus tumor (glomangioma) (*Left*) Low-power photomicrograph showing the tiny size of certain glomus tumors (*Right*) Typical glomus tumor presenting epithelioid cells with a variable collagen stroma dispersed throughout Note the numerous dilated, thin-walled blood vessels

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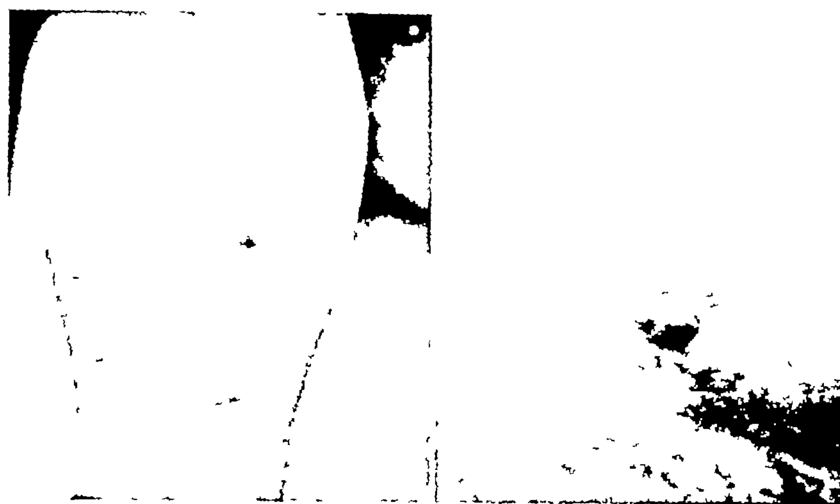


FIG 261 Clinical appearances of glomus tumors from two different patients. (Riveros and Pack, Ann Surg *133* 394, 1951 *Courtesy,* J B Lippincott Company)

marcated from the surrounding tissues and as a rule is not ulcerated

The average age of our patients was 41 years, with extremes of from 7 to 65 years There were 12 females and 8 males in this group, indicating a slight preponderance in the female sex The known duration of the tumor from estimated date of onset to the time of treatment varied from 8 months to 20 years

The locations in our 20 patients were as follows. thoracic wall, 1, temple, 1, scapular region, 1, hand, 1; knee, 2, arm, 2, forearm, 5, and fingers, 7 (the majority of which were subungual) The glomus tumor would be expected to occur regionally with the same frequency as the incidence of the normal glomus This neoplasm has been reported as occurring on the glans penis and vulva G V Brindley, Jr., reported the rare instance of a 29-year-old female who experienced sharp paroxysmal pain in her chest, aggravated by coughing The symptoms existed for 9 years Roentgenograms of the chest showed a spherical shadow in the posterior mediastinum Thoracotomy was done, and a large benign glomus tumor was removed, effecting a cure

The pain associated with the glomus tumor is the most pathognomonic symptom and was present in all of our patients except the 7-year-old child The pain may occur spontaneously without pressure or trauma No normal part of the body and no inflammatory lesion can approach the exquisite epicritic sensitivity of this tumor It may be intermittent in character, or it may develop only when the tumor is touched. It is often a stabbing, lancinating pain radiating from the tumor as focal point up an entire extremity Occasionally the slightest pressure from clothing, bedclothes, or a glove will precipitate a paroxysmal attack of agonizing pain The fear of such discomfort may influence the patient in adopting certain protective habits as preventive measures We have known subungual glomus tumors to be so exquisitely sensitive that a fingernail could not be cut, and the patient had shirt and coat slit along the arm and side in order to dress without inserting the hand through the sleeves. Atrophy of the entire arm and shoulder, presumably due to disuse, has occurred in an extremity containing a glomus tumor The pain is usually exaggerated in cold weather and is sometimes relieved by immersion of the part in warm or hot water Patients have observed the tumor to become more blue in color during the experience of pain

The pain of the glomus tumor may be associated with various sympathetic vasomotor disturbances such as localized

sweating or Horner's syndrome. Bailey considers the glomus tumor or glomangioma to be a functional overgrowth of the neurovascular end organs and explains the mechanism of pain as associated with dilatation of the glomic vessels. He states that in experimental animals trifling tactile or chemical stimulation of the cutaneous surface will cause the normal glomic vessels to dilate. He assumes that the paroxysms of pain are definitely associated with dilatation of the vessels of the glomus tumor The vasomotor thermal, and secretory phenomena associated with the tumor on the same extremity certainly indicate its relationship with the sympathetic nervous system.

The pin test of G Love serves a useful purpose if a glomus tumor is suspected but there is no visible lesion. The head of a common pin is gently rubbed over the approximate field, and on touching the invisible tumor the trigger point sensitivity is localized. In considering the differential diagnosis from such tumors as neurofibroma, melanoma, and angioma, Bailey has emphasized the fact that they can be seen and are usually painless whereas the glomus tumor is painful and sometimes not seen

GLOMUS TUMORS INVOLVING BONE

Whenever the roentgenologist detects a clear-cut destruction of the cortex of a terminal phalanx, a subungual glomus tumor should be suspected. It is the expansile character or pulsation of the tumor which actually erodes the bone of the underlying distal phalanx. We have observed three instances of such osteolytic glomus tumors

CASE REPORT NO 41, GLOMUS TUMOR INVOLVING BONE

A 30-year-old woman had experienced pain of five years duration centered in the left index finger The pain was aggravated by motion, and the finger required constant protection After removal of the nail and curettage, the pain persisted and became exquisite A radiograph of the finger showed decalcification and localized destruction of the dorsum of the terminal phalanx. Under local anesthesia and by a U-shaped *incision* a *small reddish* tumor was dissected from its bed in the bone with immediate and complete relief of pain

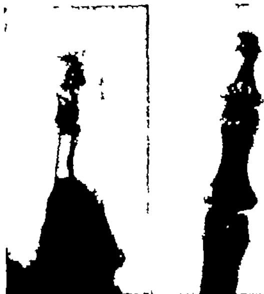


FIG. 262. Subungual glomus tumor Roentgenograms demonstrating destruction of terminal phalanx. (Riveros and Pack, Ann. Surg 133:394 1951 *Courtesy* J B. Lippincott Company)

CASE REPORT NO 42, GLOMUS TUMOR INVOLVING BONE

A 47 year-old man suffered pain of two years duration, localized in the right little finger The pain was unbearable with changes of temperature and on touching the finger The skin of the finger tip was reddish purple and showed tiny vascular dilatations An x ray examination revealed partial destruction of the bone of the distal phalanx. The pain permanently disappeared after surgical removal of the tumor

TREATMENT

Treatment of the glomus tumor by heat, cold, or sympathectomy has been without benefit. The neoplasm is radioresistant and should never be treated by irradiation. In our patients an average

TABLE 54. GLOMANGIOMA—SUMMARY OF TWENTY CASES

Case Number	*Sex & Age*	*Location*	*Size*	*Duration in Years*	*Symptoms*	*Clinical Diagnosis*	*Microscopic Diagnosis*	*Treatment & Results*
1	[illegible] 30	Right upper arm	5 mm	2	Painful nodule	Neurofibroma	Glomus tumor	Excision Relief of pain
2	M 7	Left upper arm		Recent	Tumor No pain	Hemangioma	Glomus tumor	Excision Cure
3	M 19	Left forearm	7 mm	Indefinite	Bluish nodule Whitens under pressure	Neurofibroma	Glomus tumor	Excision Cure
4	F 60	Left forearm	1 cm	20	Red tumor Exquisite pain (Wore short sleeves)	Glomus tumor	Glomus tumor	Excision Cure
5	M 65	Right knee		15	Extremely painful tumor Disabling Syncope on tumor pressure (Brother also had glomangioma)	Glomus tumor	Glomus tumor	Excision Cure
6	F 10	Left forearm	2 5 mm	8 mo	Very painful tumor	Glomus tumor	Glomus tumor	Excision Cure
7	M 12	Right forearm	5 mm.	3	Red tumor Painful	Glomus tumor	Glomus tumor beneath pigmented nevus in skin	Excision Cure
[illegible]	[illegible]	Left forearm	5 mm.	5	Red tumor Very painful	Cavernous hemangioma	Glomus tumor	Excision Cure
[illegible]	[illegible]	[illegible] wall		15	Painful bluish tumor	Glomus tumor	Glomus tumor	Excision Cure
[illegible]	[illegible]	[illegible] knee	2 cm	7	Painful bluish tumor	Glomus tumor	Glomus tumor	Excision Cure
[illegible]	[illegible]	[illegible] temple	3 mm	[illegible]	Painful blue tumor	Melanoma	Glomus tumor	Excision Cure
[illegible]	[illegible]	[illegible] thumb		3	Painful tumor Radiating pain	Glomus tumor	Glomus tumor	Excision Cure

Case Number	*Sex & Age*	*Location*	*Size*	*Duration in Years*	*Symptoms*	*Clinical Diagnosis*	*Microscopic Diagnosis*	*Treatment & Results*
13	M 48	Left index finger	6 mm.	3	Red painful tumor	*Glomus tumor*	Glomus tumor	Excision Cure
14	F 36	Right thumb		11	Bluish tumor Very painful. Pain radiates to neck	Glomus tumor	Glomus tumor	Excision Cure
15	M 39	Right thenar eminence			Red painful tumor	Neurofibroma	Glomus tumor	Excision Cure
16	F 40	Scapula	*5 mm*		Bluish painful tumor	Glomus tumor	Glomus tumor	Excision Cure
17	F 30	Left index finger		5	Exquisite pain Atrophy of finger X ray evidence of bone invasion	Glomus tumor	Glomus tumor	Excision Cure
18	F 47	Right little finger		2	Exquisite pain No evidence of tumor X ray evidence of bone invasion	Glomus tumor	Glomus tumor	Excision Cure
19	F 35	Left ring finger		3	Pain Skin was wine-red color X ray evidence of bone invasion	Bone sarcoma	Glomus tumor	Phalangeal disarticulation
20	F 47	Right index finger	5 mm	3	Painful tumor		Glomus tumor	Excision Cure

of 6½ years elapsed from the onset of symptoms until surgical removal was accomplished It would seem almost unbelievable that patients would tolerate the lesion so long, because pain is the presenting symptom. The explanation of this delay may be due to three facts (1) the pain may not be so severe at first and only gradually increases as time goes by, (2) the pain may long precede the clinical appearance or recognition of the tumor, and (3) the patient sometimes does not associate the lancinating, radiating pain with the small neoplasm Simple surgical excision is sufficient An unusually large amount of Novocain is needed for anesthesia Because the tumor is invariably benign, it does not recur after removal The reported instances of metastasis are questionable

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MALIGNANT TUMORS

INTRODUCTION

Malignant tumors of blood vessels although rare in comparison to the frequently observed benign blood vessel tumors, occur with sufficient frequency to warrant careful analysis in order to diagnose each of the types accurately The natural history of each form varies, necessitating different forms of treatment and offering different prognoses

On theoretic grounds blood vessel tu

mors should lend themselves well to nosologic division because they reproduce either perfect or imperfect vessels The cells which comprise the tumor are either the endothelial cells, smooth-muscle cells, or the pericytes about the adventitia of the vessels The tumors are listed according to the predominating cell type Frequently, however, it is impossible to identify the cell of origin, and we have listed such malignant blood vessel tumors as angiosarcoma Kaposi's hemorrhagic sarcoma represents a complex tumor of blood vessels containing vascular elements admixed with fibrosarcomatous elements

The classification of the malignant vascular tumors is further complicated by the fact that lymphatic elements may either be intermingled with the vascular constituents or else it may not be possible to distinguish the lymphatic from the vascular components This was exemplified in one of our cases (case report No. 53) of lymphangiosarcoma developing in a lymphedematous extremity subsequent to radical mastectomy This case, originally diagnosed as Kaposi's hemorrhagic sarcoma by Dr Fred W. Stewart, was later rediagnosed as lymphangiosarcoma

ANGIOSARCOMA*

Angiosarcomas are malignant tumors of blood vessels which are being reported with increasing frequency. The exact incidence is unknown because of confusion regarding their classification It is likewise difficult to derive statistical satisfaction from the cases reported in the literature, because of ambiguity in terminology and uncertainty regarding precise histologic classification Accordingly, for the purpose of this presentation, 20 patients bearing angiosarcoma were assembled from all the services at Memorial Hospital, and the results gleaned from this analysis are herewith presented

The microscopic diagnosis in each case was made either by Dr Fred W Stewart or the late Dr James Ewing in simple, factual terminology Present micropathologic findings are not sufficiently conclusive to permit unequivocal, highly specific terms Confusion probably will not end until large series of cases are reported with well-founded, factual terminology and are histologically substantiated at some future time with in vitro tissue cultures Certain subvarieties of malignant vascular tumors such as granulation-cell sarcoma, hemangioendothelioma, and hemangiopericytoma will be independently discussed

Although angiosarcoma has been regarded as a very rare neoplasm, recent indications point to a higher incidence than was previously supposed This information has been well developed by Kinkade, who reviewed the literature from 1934 to 1949 The true incidence is not known, but it is noteworthy that at Memorial Hospital in a 10-year period 1,056 cases of benign angioma were recorded and that during this same 10-year period there were recorded 20 cases of angiosarcoma and 36 cases of Kaposi's sarcoma These figures probably present a fairly accurate percentage relationship of the benign and malignant vascular tumors In addition, 27 specimens of angiosarcoma were also submitted to Dr Stewart and Dr Ewing from other sources over the same 10-year interval, but these cases are not included in this discussion

Angiosarcoma, when studied comparatively with Kaposi's sarcoma (discussed in the following division of this chapter), revealed several interesting parallels in clinical incidence, distribu-

* In collaboration with William D McCarthy



FIG. 263. Angiosarcoma of the hand and wrist. (*Upper*) Photograph of tumor 4 months following trauma to the region. There was no clinical evidence of tumor preceding trauma. (*Lower*) Hemisection of amputated arm, demonstrating extent of the tumor (McCarthy and Pack, Surg. Gynec. & Obst. *91* 465 1950. *Courtesy* Surgery Gynecology and Obstetrics.)

tion and behavior A racial predilection for Kaposi s sarcoma in the Jewish and Italian population for example, was noted also to obtain for angiosarcoma Of 20 angiosarcoma patients 14 were Jewish and 1 was Italian a total of 75 per cent as compared to the 83 per cent total for Kaposi s disease. Angiosarcoma, however unlike Kaposi's sarcoma, appeared to afflict both sexes equally 11 (55 per cent) were males and 9 (45 per cent) females It occurred more frequently in childhood and youth. Whereas 78 per cent of the patients with Kaposi s sarcoma developed the disease after the age of 40 14 (70 per cent) of the angiosarcoma cases had their onset before the age of 40 A majority of 45 per cent occurred in the ages between 10 and 30 The highest incidence in the group of patients with Kaposi's sarcoma was in the fifth and sixth decades

DISTRIBUTION

The anatomic distribution of the primary lesion of angiosarcoma was more diverse than that of Kaposi's sarcoma but nevertheless showed the same tendency to occur on the extremities However it developed generally as a tumor of the soft parts rather than of the skin. Approximately 55 per cent of the angiosarcomas occurred on the extremities as compared to 87 per cent of the primary Kaposi's sarcomas The exact anatomic distribution was lower extremity, 7 (35 per cent) paranasal region, 5 (25 per cent) upper extremity 4 (20 per cent) breast 2 (10 per cent) and head and neck, 2 (10 per cent) A similar pro-

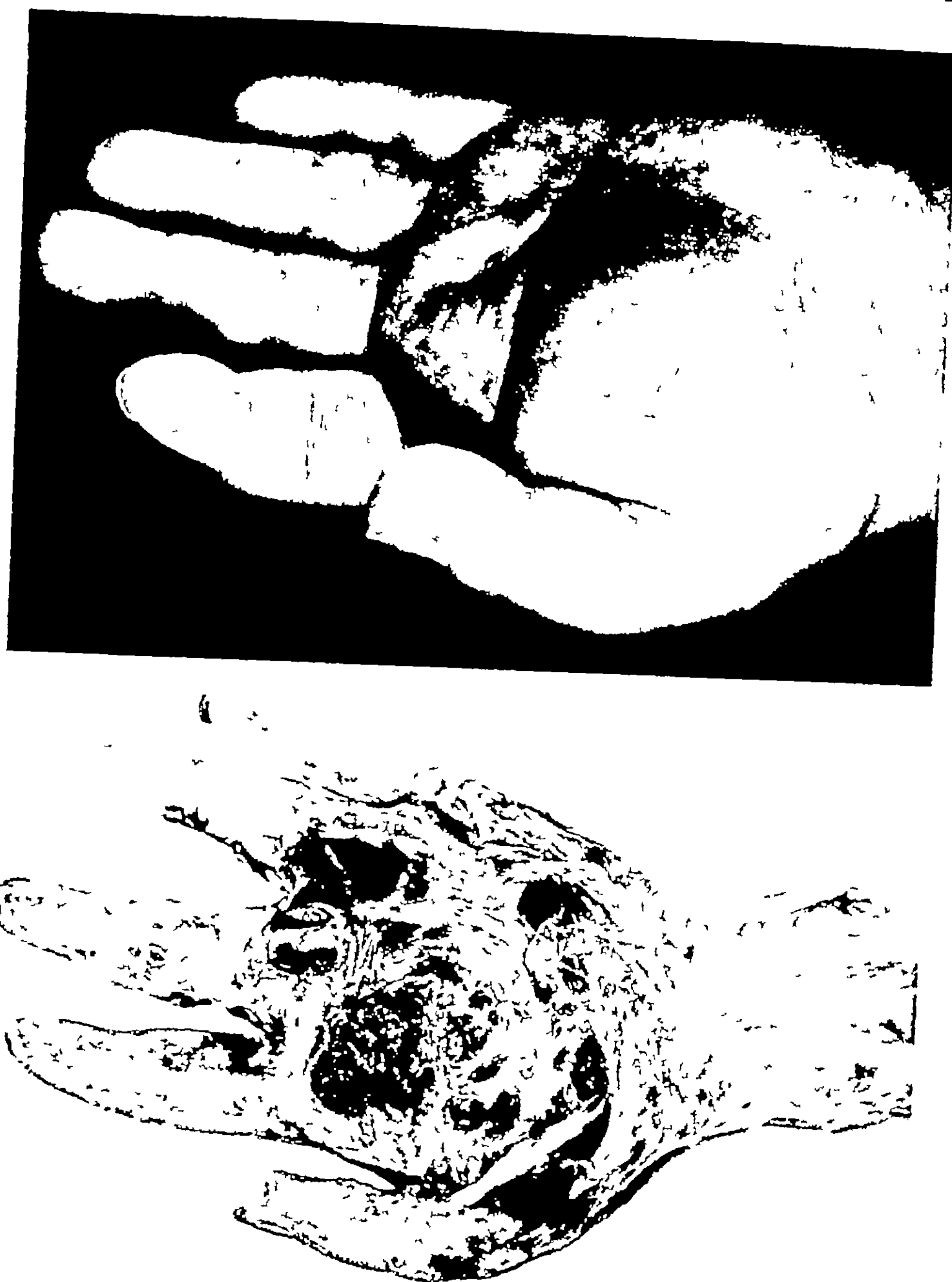


FIG 264 Angiosarcoma of the hand (*Upper*) Bulky, firm, fixed tumor necessitating amputation (*Lower*) Hemisection of resected specimen, revealing hemorrhagic nature and extent of the sarcoma (McCarthy and Pack, Surg Gynec & Obst *91* 465, 1950 *Courtesy*, Surgery, Gynecology and Obstetrics)

pensity for extremities was observed also in the 27 additional submitted specimens and in the series reported by Schmidt

ETIOLOGY

Little is known about the etiology of angiosarcoma except in a fragmentary way Trauma, verified by medical records, was a declared factor in onset in three of our patients and in two cases reported by Stout One therefore is logically compelled to consider the genesis of angiosarcoma from the granulation-tissue capillaries of traumatized tissues In two of our patients, aged 2½ and 16 years, medical records attested to the appearance of a mass in the injured area within two months Both died within two years of metastases from a primary angiosarcoma and granulation-tissue angiosarcoma of the hand and the temple, respectively A third patient presented

a similar sequence and submitted to amputation of the arm for a sarcoma of the hand. Angiosarcomas may form in regions of congenital lymphangiomatosis

PATHOLOGY

The angiosarcomas usually occurred as solitary firm, bulky tumors situated deep in soft tissue, circumscribing resistant tendons and bone but invading muscle, fat and veins as a rule (Figs 263 and 264) Occasionally angiosarcomas do invade the veins from which distant tumor emboli originate (Figs. 265 and 266) Growth as a rule, was moderately rapid, and hemorrhagic cystlike cavities, necrosis and mucoid degeneration were common. Resultant pressure symptoms caused pain and tenderness

The histologic diagnosis was reconfirmed in many of the patients by repeated biopsies, long clinical follow up studies and necropsies Variations in the microscopic picture are numerous and complex, and diagnosis is difficult. As the sarcoma characteristically progresses into anaplastic phases it is often necessary to review the earlier differentiated sections and resort to silver reticulin stains The individual cells may be fusiform rounded, or polygonal. They may simulate cavernous vascular sinuses or the pseudorosettes of Ewing's tumor or may form solid sheets of cells Occasionally they exist in a delicate framework of reticulin fibers which can be closely duplicated by metastatic clear cell renal adenocarcinoma. Three angiosarcomas were found microscopically to resemble Kaposi's sarcoma.

CLINICAL COURSE

The clinical course of the patients with angiosarcoma varied and was determined by the type of sarcoma, its location, and aggressiveness The tumors



FIG. 265 Angiosarcoma. Photomicrograph showing invasion of popliteal vein by sarcoma of the leg Note lumen of vein at the left of photomicrograph. (McCarthy and Pack, Surg Gynec. & Obst. 91 465 1950 *Courtesy* Surgery Gynecology and Obstetrics.)

in the extremities were characterized by rather rapid onset and growth, bulky tumefaction pain and associated edema. The onset of angiosarcoma in the nasal cavity and sinuses generally was accompanied by epistaxis headache, nasal obstruction with gradual swelling and displacement of the eye and destruction of bone. The sarcomas in the breast developed rapidly as large tumors and showed aggressive growth Death in most cases ensued within three years from metastases to lungs viscera, bone, and lymph nodes

TREATMENT AND PROGNOSIS

The therapy of the patients in our series was diverse and varied according to the site and stage of disease In general the majority received extensive x ray or radium therapy frequently with

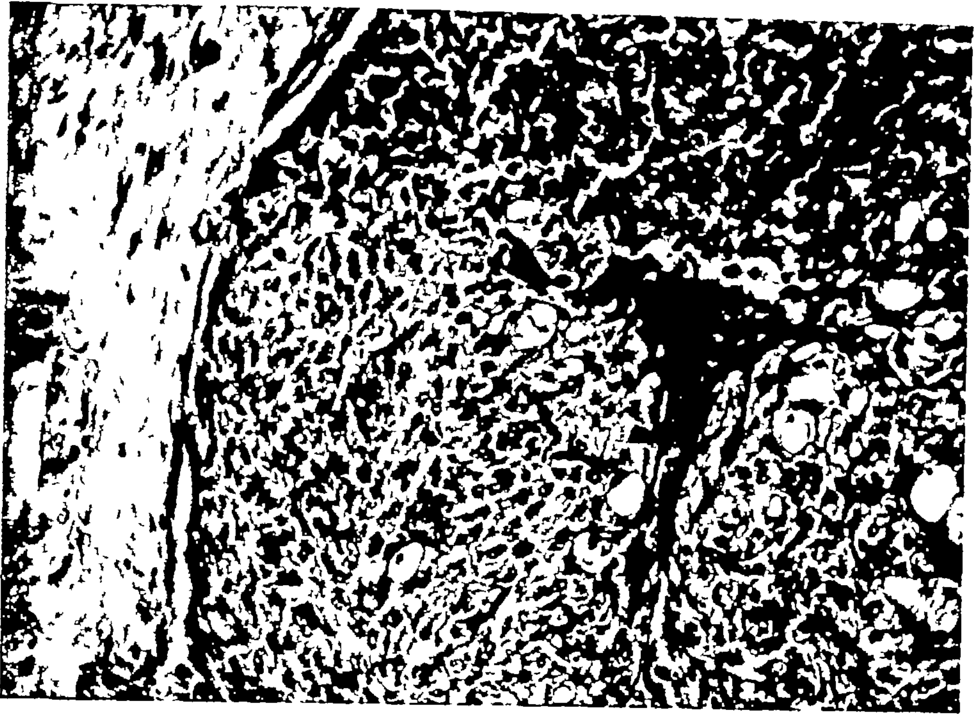


Fig 266 Angiosarcoma in vein Note wall of vein at left of photomicrograph

radical surgery Definite conclusions have been formulated but are complicated by several patients who had been previously treated and were admitted in advanced stages of cancer dissemination



Fig 267 Angiosarcoma in bone In this photomicrograph the presence of cavernous vascular sinuses is to be observed (McCarthy and Pack, Surg Gynec & Obst *91* 465, 1950 *Courtesy*, Surgery, Gynecology and Obstetrics)

Consider first the total of 11 patients with *sarcoma of the extremities* It was noted that 9 had previous local excision elsewhere Amputations were performed on 4 patients, but analysis revealed an average delay of 14 months after local excision before they were referred for radical surgical treatment, 3 of these patients died, and 1 is alive and well The remaining 7 patients of this group delayed 17 months on an average before referral and admission, and in them the sarcomas were moderately advanced All 7 patients in the group received x-ray therapy, and 3 were also treated by wide excision of the tumor In this group of 7 patients, 4 expired, 1 was alive and well for one year, 1 was alive with residual sarcoma 18 months, and 1 was lost to follow-up Although the primary and metastatic lesions were moderately radiosensitive, there were no 3-year or 5-year "cures" among the patients treated by irradiation Although irradiation did not appear to prolong life, it added materially to the comfort of the patient by the palliation of pain

It is our studied opinion that irradiation should be reserved as a *palliative*

procedure for advanced cases Local excision or wide excision of the tumor is definitely contraindicated, not only because of the danger of dissemination but also because the procedures are inadequate and serve to delay the real *curative* course of therapy which is prompt amputation. Furthermore since 45 per cent of the determinate cases developed lymph node metastases it is logical to consider interscapulothoracic amputation, hip-joint disarticulation with deep iliac node dissection or hemipelvectomy in order to encompass metastases in axillary inguinal, and iliac nodes.

The second most common tumor site in the series was the *nasal cavity and sinuses* The 5 patients in this group constituted 25 per cent of the series Therapeutic results here were more encouraging, due probably to the low grade nature of the tumors and a shorter interval of delayed admission The youngest patient, 13 years old, presented an aggressive angiosarcoma of the paranasal region which involved nares orbit, and sinuses and was radio-resistant. The benign analog of this tumor is the juvenile nasopharyngeal angiofibroma which occurs in boys Intensive x ray therapy was ineffective and the patient was lost to follow up Again hereditary and racial predilections must be considered, since the boy was Jewish and had a tragic family history of cancer His 2-year-old sister died with sarcoma of the buttock, and his father and mother died with cancer of the oral cavity and esophagus The oldest patient, aged 71 years was treated with 3250 mc. hrs of intranasal radium for angiosarcoma of the posterior nasal cavity and was free of cancer five years later A third patient, aged 56 with a radio-resistant polypoid sarcoma of the ethmoids was alive with cancer two years after intensive x ray treatment. The 2 remaining patients were young women, 29 and 22 years of age The older patient delayed medical consultation 18 months and responded poorly to radical antrotomy and irradiation. She survived four years The 22 year-old patient was free of sarcoma three years after high-voltage x ray therapy for capillary angiosarcoma of the nares



FIG. 268. Angiosarcoma of antrum in a 13-year-old boy (*Courtesy* Dr Hayes Martin. McCarthy and Pack, Surg Gynec. & Obst. *91* 465 1950 *Courtesy* Surgery Gynecology and Obstetrics.)

The onset of the cancer in the two young women was particularly interesting, because it occurred during pregnancy in both. It has been previously observed that similar hormonal growth stimulation of hemangiomas occurs during pregnancy and the menarche. Recent investigations appear to relate such vascular phenomena during pregnancy to high estrogen levels.

Angiosarcoma of the breast was noted in two young female patients One patient, aged 18 presented the rare type of capillary angiosarcoma, or "metastasizing hemangioma" which microscopically may resemble a benign, orderly hemangioma but clinically behaves as a sarcoma. The course of this patient is described in case report No 43.

The second patient, aged 23, noted a rapidly growing mass in the breast after



Fig 269 Angiosarcoma of the breast Photomicrograph of section with pseudo-rosettes resembling Ewing's tumor (McCarthy and Pack, Surg Gynec & Obst *91* 465, 1950 *Courtesy,* Surgery, Gynecology and Obstetrics)

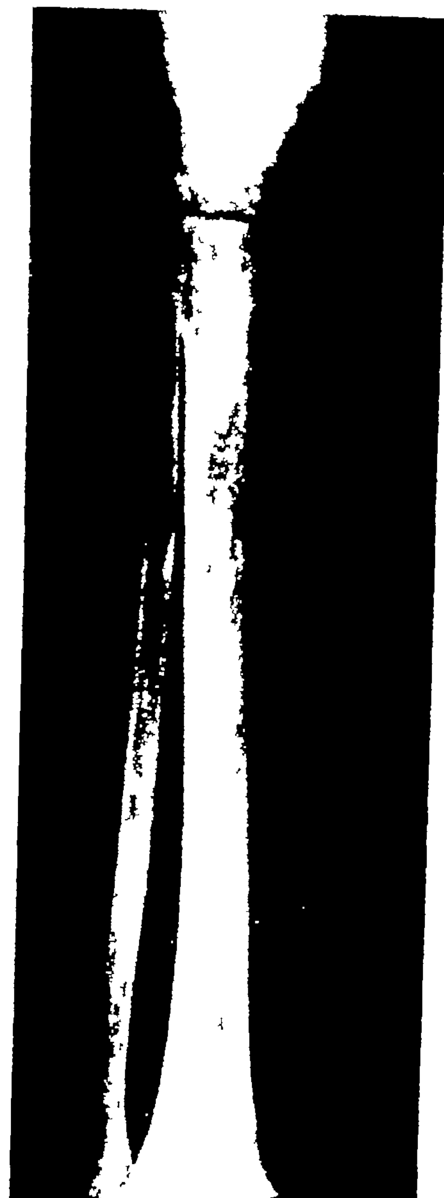


Fig 270 Roentgenogram showing angiosarcoma metastatic to bone

two episodes of trauma to the region The mass was locally excised twice by her physician, and a radical mastectomy was finally performed four months after onset Postoperative x-ray therapy was ineffective for local recurrence, and the patient died of pulmonary metastasis within one year after onset (Fig 269)

In the final group there were two patients with primary angiosarcomas on the *temple* and the *neck* In one patient, a 2½-year-old girl, a sarcoma developed in the site of a hematoma of the temple one month after injury from a fall The tumor was excised by her physician four months after onset, and the biopsy was reported as granulation-cell sarcoma The patient expired two years after onset, and postmortem examination demonstrated metastases to cervical, thoracic, and abdominal lymph nodes and bone The second case, a 34-year-old male, developed a tumor of the upper neck which was originally excised and again removed on two subsequent occasions when it recurred eight and ten years later The tumor finally recurred twenty years after onset and only then was biopsied The biopsy was reported as angiomyosarcoma The patient was alive with cancer when examined seven months later Presumably the early recurrences were those of a benign tumor which finally evolved into a true sarcoma after a long latent interval On occasion a metastasis from an angiosarcoma to bone may herald the malignant metastasizing nature of these neoplasms (Fig 270)

Contrary to the generally accepted opinion, there is evidence in our series that benign angiomas can and do pro

gress into angiosarcoma, particularly following radiation therapy Three patients with benign angiomas verified by biopsy later developed angiosarcoma in the identical regions One patient a 33-year-old female, had an angioma of the thigh treated elsewhere by x rays at the age of 15 It recurred fifteen years later as an angiosarcoma. The remaining two patients, both aged 35 submitted to excision of benign lymphangiomas of the leg four years and twelve years prior to the final biopsy which indicated lymphangiosarcoma in both instances Both patients had received postexcisional x ray therapy over the scars

Angiosarcoma proved to be a more lethal disease than Kaposi's sarcoma and terminated in death in a shorter time. The average survival interval from the onset to time of death was 2½ years for angiosarcoma as compared to 8 years for Kaposi s disease In the patients with Kaposi s sarcoma, the 5-year-cure rate was 19 per cent however several patients were alive with the sarcoma for 10 to 25 years The 5-year-cure rate for the patients with angiosarcoma was 9 per cent, and the 3-year-cure rate was 17 per cent.

In summarizing this comparative survey of angiosarcoma and Kaposi s sarcoma, several conclusions seem warranted. Definite predilections in race, sex, and anatomic onset were noted with Kaposi s sarcoma. Among our patients 82 per cent were Jews and Italians 92 per cent were males, and 87 per cent had their onset on the extremities The neoplasm was bizarre or fulminating in females Similar predilections were noted in the patients with angiosarcoma. Three of the patients with Kaposi s sarcoma also had lymphoblastoma (see p 465) Angiosarcoma was observed to develop from irradiated benign angiomas after long intervals in three patients Trauma appeared possibly to be involved in the development of angiosarcoma in five patients Prompt radical amputation was deduced to be the only curative therapy for angiosarcoma of the extremities A majority of our patients were withheld from amputation on an average of 17 months by temporizing procedures of inadequate excision or irradiation X ray and radium therapy are indispensable in the palliative treatment of angiosarcoma and Kaposi s sarcoma. The 5-year-cure rate for patients with angiosarcoma is 9 per cent the average survival interval was 2½ years The definitive 5-year-cure rate for Kaposi's sarcoma was 19 per cent, the average survival from time of onset was 8 years However several patients were alive with residual Kaposi s sarcoma from 10 to 25 years

CASE REPORT NO 43: MALIGNANT METASTASIZING ANGIOSARCOMA OF BREAST

S S., an 18-year-old girl, had observed a small lump in the left breast for several months. She sustained a rather severe blow to the breast and immediately noticed a rapid enlargement of the mass until it became the size of a small orange A local excision of the tumor was performed in another institution, and a diagnosis was made of nonmalignant angioma of the breast Two and one-half years later the patient experienced the following signs and symptoms hemoptysis severe headache, nausea, diplopia and slight hemiplegia. Neurologic examination revealed evidence of cerebral metastases in multiple foci A roentgenogram of the chest showed numerous pulmonary metastases.

A review of the microscopic character of the original tumor was made by Dr James Ewing whose diagnosis was "malignant metastasizing capillary angioma." Palliative irradiation was given but death occurred within four months On postmortem examination metastatic tumor nodules were hemorrhagic and necrotic through infarction On microscopic section they were found to be typical of malignant metastasizing capillary angioma and were present in the lungs, omentum mesentery and ovaries

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KAPOSI'S HEMORRHAGIC SARCOMA*

Kaposi's sarcoma, or "idiopathic multiple hemorrhagic sarcoma," was first described as a clinical entity by Kaposi in 1872 and is more common than the literature would indicate We quote Kaposi's original description of the disease "There develops on the skin, without known cause, either general or local, brown-red to blue-red nodules of the size of a grain of wheat, a pea or a hazelnut Their surface is smooth, their consistency densely elastic Often they are swollen like a sponge filled with blood" Although many cases throughout the world are undoubtedly unreported or unrecognized, over 800 case histories have been published to date, but inasmuch as the majority are isolated case reports, a concise correlation of data has been difficult It now appears that the disease moves through a wide range of histologic and clinical variations, largely influenced by racial and hormonal factors in the authors' opinion, all of which further complicates simple classification

* In collaboration with William D McCarthy

DEFINITION

Kaposi's sarcoma is a true but atypical sarcoma which generally has its onset as a single bluish-red macule on the extremities of individuals over 40 The microscopic picture of the early macule is deceptive in that it is essentially inflammatory in appearance with little to suggest its invariable progression into ultimate sarcoma As the macules slowly multiply and coalesce into indurated plaques, the disease gradually involves both lower extremities symmetrically in a "stocking" distribution, spreading to the trunk and finally appearing in the viscera Recent publications indicate that Kaposi's sarcoma of the viscera and lymph nodes may precede the classic skin lesions and may even cause death

without any cutaneous manifestations whatever Synonyms for the disorder are tabulated in Table 55

TABLE 55 SARCOMA IDIOPATHICUM MULTIPLEX HAEMORRHAGICUM (KAPOSI, 1872) SYNONYMS

1 Angiosarcoma perithehale fusocellulare
2. Angiosarcoma pigmentosum
3 Primitives haemorrhagisches acrosarcoid
4. Acrosarcoma multiplex cutaneum telangiectoides
5 Acroangioma hemorrhagicum
6. Sarcomatosis cutanea idiopathica
7 Sarcomatosis primitiva telangiectosica
8. Granuloma multiplex hemorrhagicum
9 Sarcoma cutaneum teleangiectaticum multiplex
10 Angioendothelioma cutaneum
11 Sarcoma haemangioendotheliale intravasculare
12. Haemangioendothelioma cutaneum
13 Sarcomatosis teleangiectaticum cutanea idiopatica generalisata
14 Perithelioma multiplex nodulosum cavernosum lymphangiectoides cutaneum
15 Acroperithelioma idiopathicum multiplex cavernosum lymphangiectoides cutaneum
16 Pseudosarcomatosis teleangiectaticum Kaposi
17 Sarcomatosis multiple hemorrhagica y pigmentaria tipo Kaposi
18 Sarcomatosi cutanea multipla emorragica di Kaposi
19 Multiple idiopathic hemorrhagic sarcoma of Kaposi
20 Angiosarcoma multiplex
21 Angiosarcoma endotheliale
22 *Granuloma angiomatoides*
23 Sarcoid Kaposi
24 Acrosarcoma Kaposi
25 Systematisierte angiomatosis
26 Kaposi s sarcoma
27 Kaposi s disease
28 Angioreticuloendothelioma

The disease has a singular racial propensity for the male Jewish and Italian populations of Russia, Italy and Poland it rarely afflicts the female sex and terminates in death after intervals ranging from a few months to 25 years.

INCIDENCE AND DISTRIBUTION

The incidence and distribution of Kaposi s sarcoma according to race, nativity age, sex, anatomic onset, and survival are outlined in Table 56 The marked predilection on the basis of race, sex, and anatomic site is probably the most unique of its kind in the entire field of neoplasms and must embody some specific significance which heretofore has not been developed in the literature. The following discussion will be largely based upon our experience with 36 patients suffering from Kaposi s sarcoma.

The onset in 78 per cent of patients occurred beyond the age of 40 years and the highest incidence was observed in the fifth, sixth, and seventh decades Although the tumor is rare in adolescence, three patients developed their disease before the age of 20 All three were of Jewish or Italian extraction

As noted throughout the entire literature, this form of cancer chiefly afflicts males The ratio in our series was 92 per cent male (33) and 8 per cent female (3) as compared to a male average of 95 per cent in most reports

Inasmuch as the majority of reported cases appeared to originate in such *countries of eastern Europe as Russia*, Poland, and Italy Dörffel concluded that the dominant distribution was on a geographic rather than a racial basis Arranging our series along both racial and geographic aspects we found that 30 (83 per cent) were Jews and Italians regardless of nativity whereas arranged on a geographic basis, eastern Europe was represented by only 74 per cent, practically all of whom were Jews and Italians Also noteworthy was the fact that 22 per cent of our patients were American born. Such findings would support the more logical and plausible theory of a racial or biologic proclivity

Another striking propensity of Kaposi's sarcoma was discovered when the early

lesions of onset were grouped according to anatomic site In 87 per cent of patients, the earliest manifestations were detected in the skin of either lower or upper extremities, the vast majority arising in the hands or feet. Three patients first observed their tumors on the penis, and the remaining two patients were both females who appeared to develop their disease first in lymph nodes.

Stewart and Treves reported the development of lymphangiosarcoma in the edematous arms of six female patients whose postmastectomy elephantiasis had existed from 6 to 24 years. (See p 478) The authors speculated on a common systemic cancerogenic factor responsible not only for the angiosarcoma of the arm but also for the prior mammary carcinoma which led to the radical mastectomy Some of the patients demonstrated skin lesions which clinically and histologically resembled Kaposi's sarcoma In reviewing the older literature we were able to discover two similar cases, both females, in which cutaneous Kaposi's sarcoma originated in the lower extremities 9 and 29 years after the onset of massive lymphedema, which resulted from infection In both instances prolonged lymphedema appeared to constitute the sole known predisposing factor inasmuch as no other primary

TABLES 56 & 57 STATISTICAL COMPARISON OF 56 PATIENTS WITH MALIGNANT BLOOD VESSEL TUMORS INCLUDING 20 CASES OF ANGIOSARCOMA AND 36 CASES OF KAPOSI'S SARCOMA

Kaposi's Sarcoma (36 Patients)		*Angiosarcoma* (20 Patients)	
Racial Incidence		Racial Incidence	
Jews (16)	44%	Jews (14)	70%
Italian (14)	39%	Italian (1)	5%
Total	83%	Total	75%
Male-Female Ratio		Male-Female Ratio	
Male (33)	92%	Male (11)	55%
Female (3)	8%	Female (9)	45%
Age at Onset		Age at Onset	
Over 40 years	78%	Under 40 years	70%
Highest incidence 40 to 70 years		Highest incidence 10 to 40 years	
Anatomic Onset		Anatomic Onset	
Lower extremity (26)	73%	Lower extremity (7)	35%
Upper extremity (5)	14%	Upper extremity (4)	20%
Penis (3)	8%	Paranasal areas (5)	25%
Lymph nodes (2)	5%	Breast (2)	10%
		Head and neck (2)	10%
Upper and lower extremities Total	87%	Upper and lower extremities Total	55%
Survival Interval after Onset		Survival Interval after Onset	
Average survival	8 years	Average survival	2½ years
Five-year-cure Rate		Five-year-cure Rate	
Free of disease (3 of 16 determinate cases)	19%	Free of disease (1 of 11 determinate cases)	9%

The occupations of the patients were too diversified to support the common belief that this sarcoma is peculiar to the laboring classes However, in the present series a prevalence of occupations which kept the patient on his feet for long intervals was noted This may be significant in view of the fact that 26 (73 per cent) patients developed their initial tumor on the feet or legs, often with associated edema Recent studies now tend to point to lymphedema as a factor in the genesis of angioblastic sarcomas

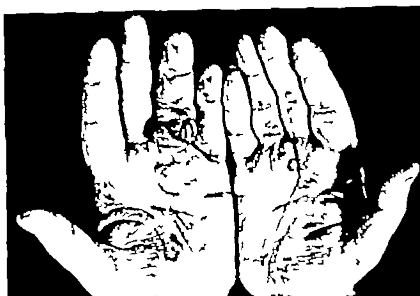


FIG. 271. Kaposi's hemorrhagic sarcoma. Multicentric origin on palms. The neoplasms are in the macular and nodular stages. (McCarthy and Pack, Surg. Gynec. & Obst. 91:465, 1950. *Courtesy* Surgery, Gynecology and Obstetrics.)



FIG. 272. Kaposi's hemorrhagic sarcoma of feet. Clinical photographs of three different patients illustrating the nodular or granulomatous phase.

TABLE 58 LOCATION OF VISCERAL LESIONS OF KAPOSI'S DISEASE (CHOISSER AND RAMSEY)

Most Common (In Order)	*Frequent*	*Uncommon*	*Rare*	*Never Recorded*
Gastrointestinal tract (all portions)	Faucial tonsil	Spleen	Heart	Brain
Liver	Bones	Pancreas	Pericardium	Thyroid
Lungs	Larynx	Kidneys	Central nervous system	Ovaries
Lymph nodes	Conjunctiva	Adrenals	Peripheral nerves	Uterus
Retroperitoneal		Peritoneum	Tongue	
Mesenteric		Testes	Bladder	
		Epididymes	Muscles	
		Trachea	Pituitary	
		Bronchi		
		Pleura		

neoplasm had previously been detected In our opinion certain of the lymphangiosarcomas of an upper extremity developing in surgical elephantiasis are truly identical with Kaposi's sarcoma In fact, Dr Stewart so diagnosed the skin nodule, submitted to him by one of us, which had been taken from our patient included in the above-mentioned six cases

ETIOLOGY

Since the original description of the disease, there have been few contributions to a better understanding of its etiology Acute systemic diseases, trauma, tuberculosis, and syphilis have been discarded as causative agents Despite the typical microscopic evolution of each Kaposi's sarcoma lesion from an inflammatorylike phase through a granulomatous phase into true neoplasia, as described by MacKee and Cipollaro, no bacteriologic or viral agent has ever been isolated Reinoculation of patients with their own tumor tissue by Pack and animal inoculations by Nesbitt, Choisser, and Ramsey failed to induce tumors at the sites of inoculation. These and other experiments have somewhat nullified the concept that the tumor is an infectious granuloma

Although a solution to the question of etiology is far from being found, recent advances in the general field of cancerogenesis make it plausible now to suspect some systemic cancerogen acting upon the vascular tissues as a possible agent Such an hypothesis would more logically explain the distinctive tendency of Kaposi's sarcoma to involve the legs bilaterally and symmetrically, ultimately to manifest itself throughout the viscera with multiple adjoining tumors in the inflammatory, granulomatous, and sarcomatous phases, and to resemble multicentric foci rather than metastases It is now possible to induce similar angiosarcomas in animals with injections of chemical cancerogens Andervont, White, and H L Stewart have induced numerous benign and malignant angiomatous tumors, several of which behaved as primary tumors of multicentric origin, with the administration of azo compounds and hydrocarbons to mice Andervont also determined that female mice were far more susceptible to such induction than males and clearly established the influence of sex hormones by markedly reducing tumor induction with castration and testosterone pellet implants Further evidence of a systemic factor in humans are the early proliferative changes of Kaposi's sarcoma in liver, spleen, and lymph nodes, which are far removed from the gross and ob-

vious sarcomatous nodules in the skin and which were well described by Stats and Tedeschi.

Undoubtedly other etiologic influences are in operation and it is essential to consider hereditary vascular dysplasias in view of the racial preponderance in Jews and Italians Tedeschi has emphasized the relation of vascular dysplasias to Kaposi's sarcoma while Watson and McCarthy noted a parallel racial preponderance of Jews in their series of hereditary familial telangiectasis (Rendu Osler Weber's disease) Cognizance must be taken of sex hormones, since the incidence of male patients with Kaposi's disease is so high. In this respect Watson and McCarthy reviewed 1 056 cases with hemangioma and demonstrated a female incidence of 65 per cent. They also observed definite growth stimulation of angiomas at the onset of pregnancy and the menarche. Further many of the female patients with Kaposi's disease have manifested its most bizarre forms and one of the most fulminating cases reported was an Italian female who survived only 34 days after onset of skin lesions

CLINICAL COURSE

In the great majority of patients, Kaposi's sarcoma originates in the skin



FIG. 273. Anterior and lateral views of a patient with Kaposi's hemorrhagic sarcoma, diffuse, macular cutaneous lesions.



FIG. 274. Kaposi's hemorrhagic sarcoma. (*Left*) Primary or macular phase. Tumor on dorsum of foot. The tumor is flat and of a violaceous hue. (*Right*) Second, or nodular stage. Tumor on medial side of knee. The tumor is sharply circumscribed, firm, and red (McCarthy and Pack, Surg Gynec. & Obst. 91 485 1950 *Courtesy* Surgery Gynecology and Obstetrics.)

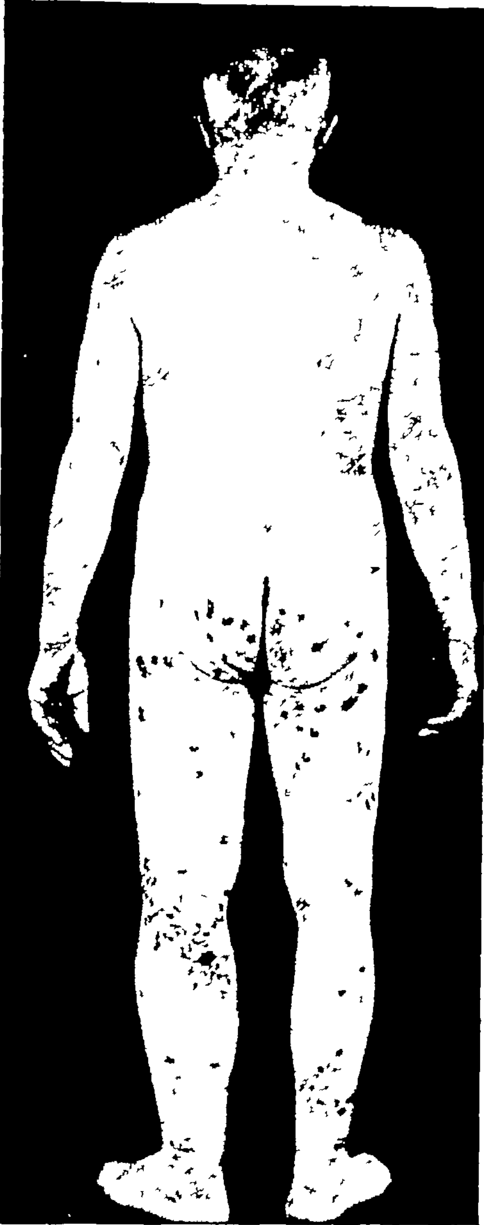


FIG 275 Kaposi's hemorrhagic sarcoma Typical diffusion of the tumors over the buttocks and lower extremities Associated lymphedema of extremity, which may precede the cutaneous lesions (McCarthy and Pack, Surg Gynec & Obst *91* 465, 1950 *Courtesy*, Surgery, Gynecology and Obstetrics)



FIG 276 Kaposi's hemorrhagic sarcoma, showing multicentric origin on feet Macular phase on left foot, third or malignant phase on right foot

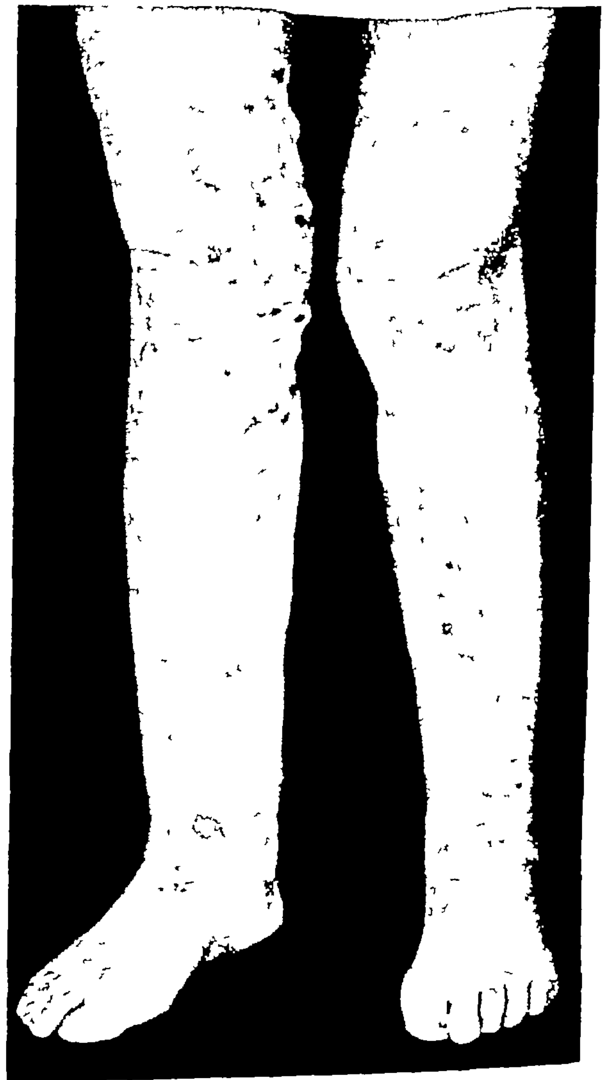


FIG 277 Kaposi's sarcoma in a female The legs and feet are markedly edematous and the lesions of Kaposi are sporadically distributed throughout the lower extremities Note the extensive varicosities which preceded the tumors

and is so typical in appearance that it can generally be diagnosed by inspection. The initial lesion appears in the skin of the extremities as a reddened, well-demarcated macule or nodule The disease appears to be more aggressive in patients with considerable vascular disturbances of the extremities

As the insensitive, early macule progresses and becomes elevated, the color darkens to a bluish red representative of the angiomalike vessel sinuses of the

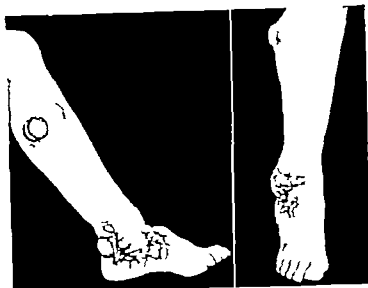


FIG. 278. Kaposi's hemorrhagic sarcoma of foot and leg of a white female (lateral and anterior views) The massive, nodular type is illustrated. This neoplastic entity seldom occurs in females. (McCarthy and Pack, Surg Gynec. & Obst. 91 465 1950 *Courtesy* Surgery Gynecology and Obstetrics.)

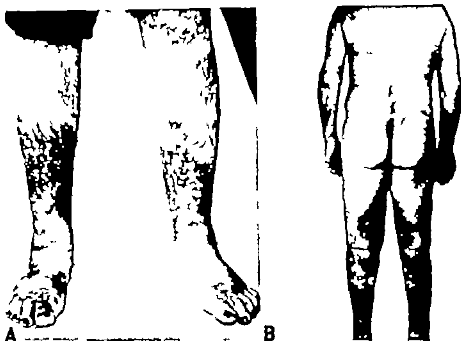


FIG. 279 Kaposi's hemorrhagic sarcoma. A. Bilateral multicentric origin on foot and legs. B Butterfly distribution on thighs. (McCarthy and Pack, Surg. Gynec. & Obst. 91 465 1950 *Courtesy* Surgery Gynecology and Obstetrics.)

granulomatous phase. The bluish-red nodules in this phase may closely simulate malignant melanoma. After many months the tumors multiply in adjoining areas as a unilateral process become more cellular and less vascular and finally attain the indurated sarcomatous phase as elevated, coalescent bluish black plaques which are several centimeters in diameter Coincidentally the disease usually involves symmetrical areas in the other extremity in "stocking" or "glove" fashion, and later extends centripetally to the trunk. As the subcutaneous tissues are diffusely infiltrated by the hemorrhagic, verrucous plaques massive edema of the extremity ensues, and the tumors *occasionally* ulcerate



FIG 280 Advanced Kaposi's hemorrhagic sarcoma of lower extremities This young Italian boy was bedridden with a useless right extremity, massive tumor involvement of the groin, irremedial odor, and chronic sepsis Right hemipelvectomy afforded great palliation with ambulation and relief for two years (Pack and Ehrlich, Ann Surg *124* 1, 1945 *Courtesy,* J B Lippincott Company)

and bleed As a rule, with the exception of the tumors on the soles of the feet and the penis, pain is not associated with the disease process

Variations of the above classic macule, nodule, and plaque are not infrequent One type evokes marked fibrous reaction and clinically resembles neurofibroma In one such instance the disease was rather indolent and remained localized in the leg for ten years Often an old lesion will regress into a flat, pigmented scar, in the periphery of which new nodules may develop Still another type is composed of pink translucent nodules similar to lymphangioma Lymphadenopathy is common in all phases of the disease, and the nodes may or may not contain actual tumor cells

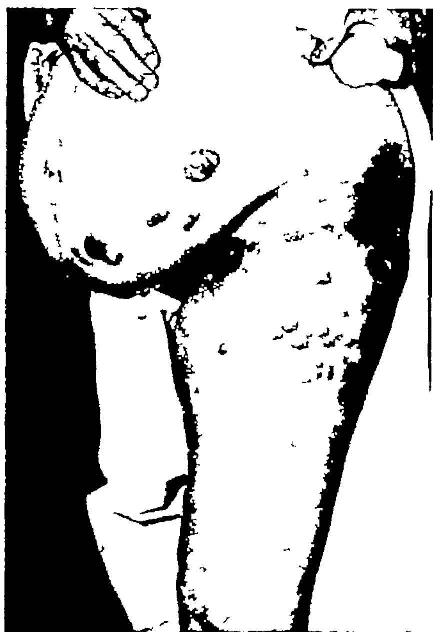


FIG 281 Kaposi's hemorrhagic sarcoma Late stage of generalization of neoplasm Numerous macular, papular, pustular, and ulcerating lesions are diffusely distributed over the body

Ultimately, the tumors may appear in the submucosa of the entire gastrointestinal tract and lungs as friable, hemorrhagic, polypoid masses This development marks the transition into a terminal phase when exitus from exsanguination is imminent Not uncommonly the tonsils, thoracic and abdominal lymph nodes, and bone are invaded by the tumor In our group extension to the oral cavity occurred in three cases, lungs, in four cases, bone, in two cases, and liver and spleen, in one case

Deviations from typical cutaneous onset have been reported, and it is now obvious that the tumor may originate in practically any part of the body However, prior to Dorffel's monograph in 1932, it was generally believed that all extracutaneous lesions were metastatic, inasmuch as up to that time few cases had been described in which the skin lesions were absent or had been preceded by visceral lesions Since then several cases have been reported with primary tumors in the viscera unassociated with any skin manifestations Primary



FIG. 282. Kaposi's sarcoma of tonsil. (*Left*) Before and (*Right*) after radiation therapy (*Courtesy* Dr Hayes Martin.) (McCarthy and Pack, Surg. Gynec. & Obst. *91* 465 1950 *Courtesy* Surgery Gynecology and Obstetrics.)

Kaposi's sarcoma thus far has been described in the heart, kidney liver intestines lymph nodes, penis eye, ear nose, and nasopharynx. Choisser and Ramsey have reported two instances of primary cardiac origin (right auricle) in which there was an absence of skin lesions The trend of evidence, therefore, would suggest that Kaposi's sarcoma may be a systemic disease of multicentric origin and long duration with little tendency to metastasize, a hypothesis which is more in keeping with the frequent 10- and 15-year survivals in the presence of active sarcoma.

Spontaneous regression of individual tumors is rare and probably follows thrombosis Long remissions also are noted and are quite deceptive to both physician and patient. One patient in the series received radium therapy for an early nodule on the sole and disappeared because regression seemed complete Six years later he re-entered the clinic with new nodules on both feet and a hand and a polypoid tumor in the tonsil.

Death generally results from progressive cachexia, intercurrent infection, or hemorrhage from friable bulky tumors in the gastrointestinal tract or lungs There was x ray evidence of pulmonary masses in four of our patients and one died of pulmonary hemorrhage. At autopsy large hemorrhagic tumors were found occluding the bronchi. In two other patients septicemia and gangrene following radionecrosis were believed to be the chief cause of death.

An interesting example of Kaposi's sarcoma which occurred suddenly at the donor site of a skin graft indicates the proclivity of damaged tissue to harbor the neoplasm, or it may represent the transplant of the neoplastic cells during the surgical procedure. (Fig 14)



FIG. 283. Primary Kaposi's hemorrhagic sarcoma of glans penis. (McCarthy and Pack, Surg Gynec. & Obst. *91* 465 1950. *Courtesy* Surgery Gynecology and Obstetrics.)

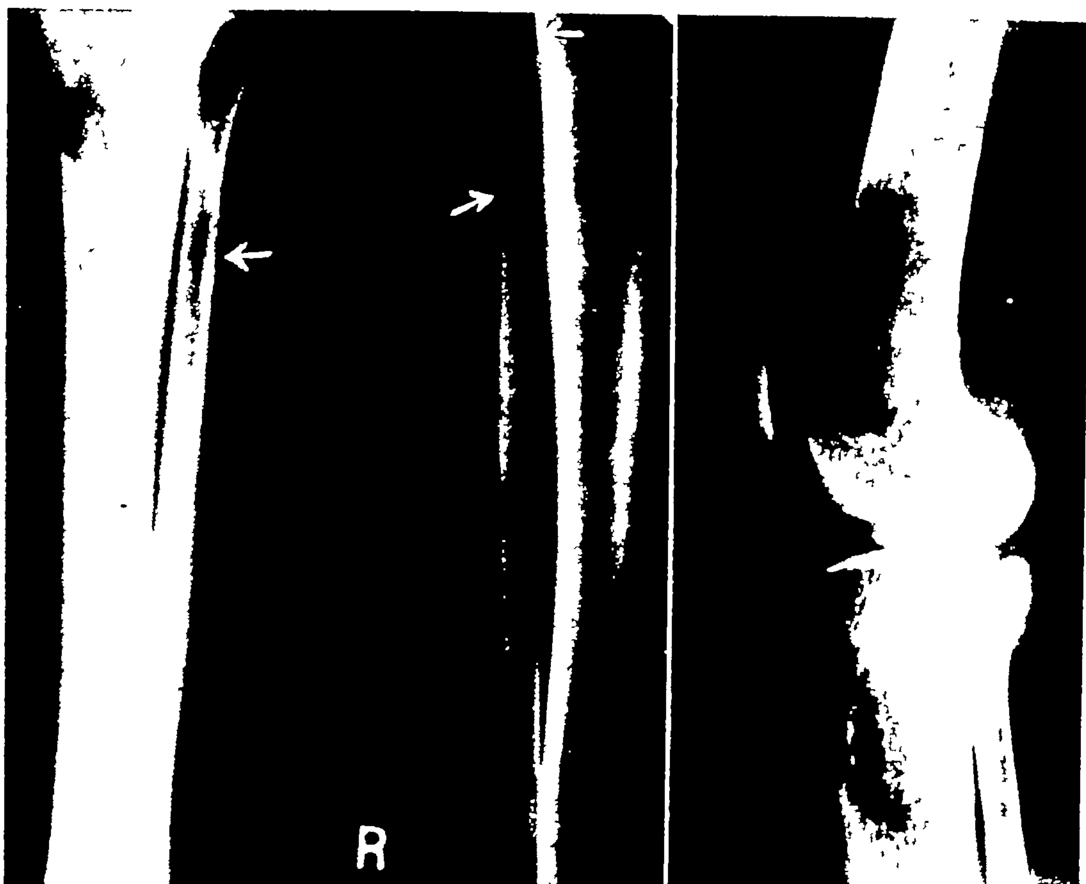


FIG 284 Metastases of Kaposi's hemorrhagic sarcoma to bone



FIG 285 Kaposi's hemorrhagic sarcoma in a Negro, a rare occurrence (Patient of Dr Lloyd Craver) (*Left*) Tumors are in the confluent nodular phase (*Right*) Same thigh 3 years later, demonstrating the regression of the tumors following low-voltage x-ray therapy (*Courtesy*, Dr Lloyd F Craver and A M A Arch Dermat & Syph *16* 35, 1927)

HISTOPATHOLOGY AND PATHOGENESIS

The histologic sections of Kaposi's sarcoma are most interesting when correlated with the clinical appearance of each lesion as it evolves from an inflammatorylike macule into the "granulomatous" bluish-red nodule resembling an angioma and into the final black plaques of frank sarcoma If sections are made of the early macule, there is little to

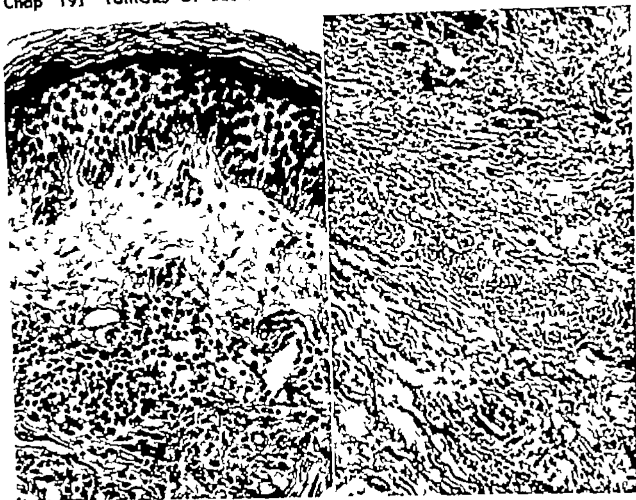


FIG 286. Kaposi's hemorrhagic sarcoma, stage one. Ectasia of vessels round-cell infiltrate. (*Left*) Section of early macule, showing process resembling inflammation or granuloma. There is little evidence of its real sarcomatous nature. (*Right*) Section of indolent lesion shown in Fig. 278 Scant angiomatous elements are present. (McCarthy and Pack, Surg. Gynec. & Obst. 91 465 1950 *Courtesy* Surgery Gynecology and Obstetrics.)

suggest its real sarcomatous potentialities The vessels of the derma are dilated and surrounded by an infiltration of round and connective-tissue cells Edema and hemorrhage are minimal. In the second phase, or granulomatous process the cardinal features are edema, hemorrhage connective-tissue proliferation and the proliferation of endothelial cells to form vessel sinuses resembling hemangiomas This attempt at new vessel formation is abnormal and imperfect and permits the escape of red blood cells into tissues, a hemorrhagic stigma which is constant in all phases of Kaposi s sarcoma. The disease ultimately progresses into the sarcoma stage as indurated, elevated black plaques which are represented by a compound picture of spindle-cell sarcoma interspersed with hemangiomatous elements and deeply stained with old blood pigment. The microscopic aspects of this sarcoma serve to re-emphasize its bizarre versatility and in some instances these wide variations may serve as an index of indolence or aggressiveness An indolent lesion in our series was represented by scant, spindle sarcoma cells encased in fibrous tissue reaction and an intermediate-type tumor by delicate cords of spindle cells interspersed with angioma like sinuses Some of the most active tumors consisted of highly cellular sheets of spindle or endothelial cells which simulated melanoma, angiosarcoma, or endothelioma.

Controversy has centered around the pathogenesis of the sarcoma for decades and continues unabated The argument wages as to whether it is (1) a true neoplasm, (2) an infectious gran

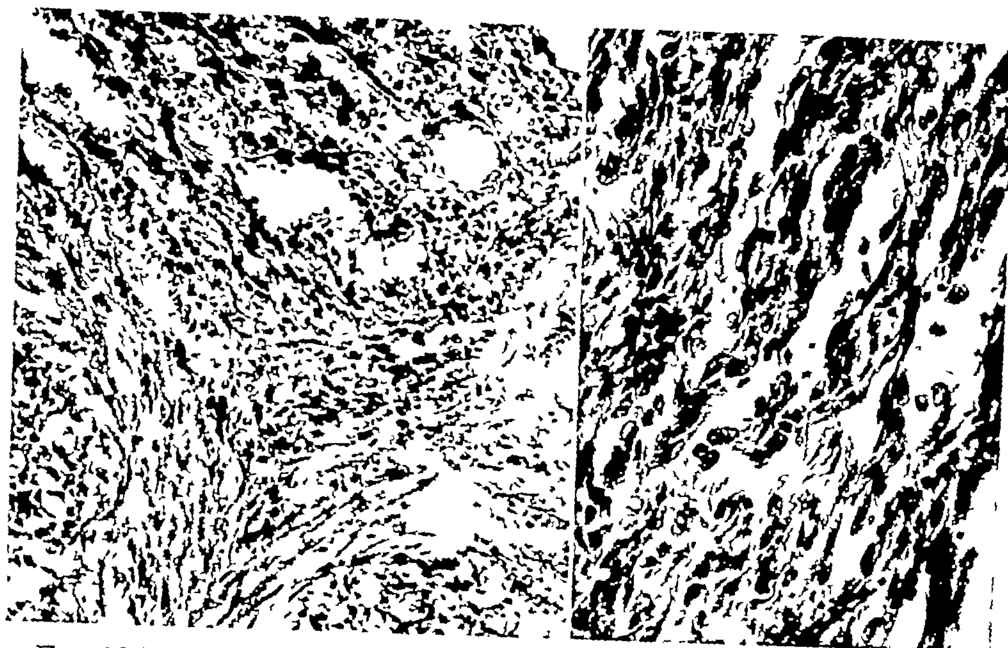


FIG 287. Kaposi's hemorrhagic sarcoma (*Left*) Mixed vascular and fibrosarcomatous pattern, final neoplastic phase This photomicrograph is a typical compound picture of spindle-cell sarcoma and angiomalike blood-vessel sinuses (*Right*) Well-differentiated vascular pattern (intermediate type), angiomatous elements present Radiosensitive tumor (McCarthy and Pack, Surg Gynec & Obst *91* 465, 1950 *Courtesy*, Surgery, Gynecology and Obstetrics)

uloma, (3) an infectious granuloma with neoplastic tendencies, or (4) a reticuloendothelial hyperplasia. Although many investigators now agree that it is a sarcoma, there is a difference of opinion as to cell origin and the ability of the tumor to metastasize All generally concede that it is of primitive blood vessel cell origin, however Plasma cells, endothelium, fibroblasts, adventitia, and vascular neuromuscular annexes have been variously advanced as tissues of origin

Kaposi's Sarcoma A Disease of the Reticuloendothelial System?

Emphasis in more recent publications, by Dorffel, Choisser and Ramsey, and Tedeschi, is on the theory that Kaposi's sarcoma is a dysplasia of the reticuloendothelial system Evidence in support of the systemic nature of the disease and its relation to reticuloendothelial origin is increasing and has been furthered by case reports of Kaposi's sarcoma coexisting with lymphatic leukemia, myelogenous leukemia, Hodgkin's disease, and mycosis fungoides Further evidence of generalized reticuloendothelial dysplasia in the patient with Kaposi's sarcoma is offered by Stats and Tedeschi who observed early microscopic deviations in tissues such as bone marrow, lymph nodes, spleen, and liver which were distant from the primary cutaneous lesions Similar changes were also observed in our microscopic sections In addition, three patients presented microscopic evidence of concomitant lymphoblastoma with their Kaposi's sarcoma, namely, Hodgkin's disease, Brill-Symmers disease, and lymphosarcoma The histologic pictures of the lesion, the multicentric development at widely located regions, the coexistence of other stigmas of diseases of the reticuloendothelial system, and the specific sites at which the lesions of both diseases are found form cogent arguments for the theory of a reticuloendothelial origin of Kaposi's disease. The earlier publications of such authorities as Alfred Scott Warthin, Kusnegow, Goldschlag, Francis Ellis, Cole and Crump, Greppi and Bettoni, and Lane and Greenwood lend support to this hypothesis The reticuloendothelial the-

ory was disputed by Ewing, who believed that Kaposi's sarcoma was a systemic disease in which a more specific structure, such as neuroarterial glomus was involved. Solution of the problem of pathogenesis is not imminent and possibly will not materialize until tissue cultures of early Kaposi tumors are investigated. A start in this direction has been made, and although results are not conclusive, tissue cultures would seem to implicate primitive mesenchymal tissue as the origin

PROGNOSIS

The prognosis of Kaposi's sarcoma should be guarded. It is difficult to evaluate properly the aggressiveness of the tumor in any individual case until many months have elapsed. Further complicating the entire outlook are the deceptive remissions, the bizarre variations in females and the unusual racial influences which render the fulminating types virtually unknown in Scandinavians and not uncommon in Italian and Jewish patients In general the course is unfavorable when cutaneous tumors rapidly involve both extremities with associated edema The outlook also is poor when lymph nodes and viscera are primarily or secondarily affected There was no relation of the age of the patient to clinical activity of the disease.

A survey of the entire group of 36 patients revealed that a total of 26 were alive only 7 in this group of living patients were free of cancer and 3 of these were 5-year "cures" who had been well for 5 6, and 9 years respectively a definitive cure rate of 19 per cent of patients treated more than 5 years ago Four in the group of 26 living patients had survived 10 11, 12, and 25 years with active cancer All had received radiation therapy

In the series of patients who died of the cancer 3 had survived 2 to 5 years 5 survived 5 to 10 years and 2 lived for



FIG. 288 Kaposi's hemorrhagic sarcoma. Sheets of solid cells simulating other types of sarcoma. This portion of the tumor is almost entirely endotheliomatous. (McCarthy and Pack, Surg Gynec. & Obst. *91* 465 1950 *Courtesy* Surgery Gynecology and Obstetrics.)

15 to 20 years One of these patients died of prostatic cancer 6 years after the initiation of therapy for Kaposi's sarcoma. The average survival interval with treatment was approximately 8 years

TREATMENT

Practically all modalities of therapy were employed in the treatment of this series of patients Enumerated, the methods were excision with scalpel and cautery radium pack, external and interstitial radon, contact x ray and 100 kv 200 kv and 240 kv x ray therapy with all gradations of factors

Although radiation therapy has been commonly recommended as the best method in most published papers to date, there has been little reference to or experience with, the surgical treatment of Kaposi's disease In our experience wide surgical excision of the *early*

solitary lesion has yielded gratifying results Analysis of the group of seven patients free of disease revealed that five had submitted to excision of their lesion at onset, one of these patients had remained entirely well for nine years The two patients whose primary macule of the penis had been treated by amputation were well for five and six years However, surgery is contraindicated if the tumors are extensive or multiple, or if edema is coexistent Invariably such edema indicates deep vessel involvement and predisposes the tissues to infection and indolent postoperative defects Occasionally, palliative cautery excision is useful for the removal of fungating tumors in the oral cavity and should be followed by intraoral x-ray therapy

Fortunately, Kaposi's sarcoma is relatively radiosensitive, and radiation is the choice of therapy if the lesions are multiple or if the process is diffusely extensive Moreover, it has been our experience that the early, more vascular macules and nodules are far more radiosensitive than the older, indurated plaques For this reason, therefore, it is essential to educate the patient in the importance of detecting and treating the tumors in the early phases In most instances the early macule and nodule will completely regress with doses of unfiltered low-voltage roentgen therapy in the range of 1000 to 2000 r A similar response is attainable with a similar dose, using radium plaques at 1 cm distance For larger, superficial regions, unfiltered low voltage x-ray is also used, employing a 100 kv machine, from 20 to 30 cm T S D , and small portals for an average of from 400 r to 800 r individual doses The bulky skin plaques required larger doses with some filtration All treated areas were noted on anatomic charts lest the pigmented regression be mistaken later for a new macule and radiated a second time, with the hazard of late radionecrosis

High-voltage roentgen therapy was reserved for the deep tumors which involved lymph nodes, mediastinum, lungs, abdominal viscera, and bone. In two patients with disease in the os calcis and tibia, the tumor regressed, and pain disappeared following 200 kv x-ray therapy Cross-fire technic was used with two small portals delivering 300 r daily at 30 cm T S D with 2 mm aluminum filters for a total dose of from 1500 to 1800 r With the exception of one dramatic regression in the treatment of splenomegaly, high-voltage x-ray therapy has been only fairly successful Nitrogen mustard has proved disappointing in the few cases treated thus far

In the final summary it cannot be too strongly emphasized that radiation therapy be given in conservative doses if the sarcoma is extensive or if edema is present In either event the blood supply is generally impaired because of the very nature of the disease Consequently, overtreatment may readily result in necrosis, infection, and gangrene For the same reason, interstitial irradiation and "blanket irradiation" with large portals are hazardous

CASE REPORT NO 44
KAPOSI'S SARCOMA PRECEDED BY LYMPHANGIECTASIS

A J , a Puerto Rican Spaniard, age 58, was first seen in July, 1942 At that time he had bilateral idiopathic hemorrhagic sarcoma involving both feet and ankles Numerous multicentric nodules of Kaposi's sarcoma in all stages of evolution were found, some of which were ulcerated and bleeding Local surgical excision was done for some of these tumors, others were treated by low-voltage unfiltered x-ray therapy and the tiny macular lesions by the application of an unfiltered radon bulb used in contact for doses of from 200 to 300 mc -min A larger ulcerated lesion on the sole of the foot was treated by surgical excision and application of a whole-thickness skin graft

In the intervening fifteen years numerous other nodules have been treated by short distance contact x ray therapy and some by surgical excision. Two separate nodules on the penis one on the foreskin and one on the glans were similarly treated, with their complete disappearance. There has been no evidence of generalization of the sarcoma to date and palliative control has been constantly maintained.

Past History

In 1926 he acquired filariasis. At that time he had the usual swelling of both legs, more marked on the right side and elevation of temperature The diagnosis was established by laboratory examination of his nocturnal blood. These episodes occurred almost yearly with fever prostration, and progressive lymphedema of the extremities. The last attack of this type occurred three years before the onset of the first evidence of Kaposi's multicentric hemorrhagic sarcoma

Comment

This case report is presented to emphasize the importance of circulatory disturbances in the extremities preceding the onset of Kaposi's sarcoma Similar cases have been reported from South Africa of the tumors occurring in Bantu natives who had vascular disturbances expressed by lymphedema of the lower extremities antedating the onset of the tumors by several years The mechanism by which lymphangiectasis predisposes to the onset of this tumor is unknown, but presumably it is identical with the onset of the peculiar multiple lymphangiosarcomas which occur in arms complicated by surgical elephantiasis secondary to radical mastectomy for mammary cancer

THE CONCOMITANT OCCURRENCE OF KAPOSI S SARCOMA AND LYMPHOBLASTOMA*

A total of seven cases of Kaposi s sarcoma collaterally existing with Hodgkin s disease, leukemia, myelogenous leukemia, and mycosis fungoides has been described in medical literature.

Three additional instances have been reported by us in which was observed the concomitant occurrence of Kaposi s sarcoma and lymphoblastoma. In two patients Kaposi's sarcoma and giant follicular lymphoma (Brill-Symmers disease) occurred concurrently a combination not previously described to our knowledge The third patient had a combined diagnosis of Kaposi s sarcoma and malignant lymphoma. A fourth patient at the onset of her disease had a microscopic picture and clinical findings simulating Hodgkin s disease but eventually developed the typical cutaneous manifestations and pathologic changes of Kaposi s sarcoma.

One of our cases (case report No 47) demonstrates the more commonly observed combination of Kaposi s sarcoma and malignant lymphoma occurring in the same patient. In case reports Nos 45 and 46 both Kaposi s sarcoma and Brill-Symmers disease are present. This would seemingly give additional scope to the conjoined occurrence of Kaposi s sarcoma and tumors of a lymphoblastomatous nature

The patient in case report No 48 is unusual from several standpoints During the early development of Kaposi s disease, the clinical as well as the microscopic picture mimicked Hodgkin s disease. (Greenstein and Conston *did* observe a patient who had coexistent Kaposi s sarcoma and Hodgkin s disease.) In our patient the first six years of her illness were manifested entirely by a generalized lymph node involvement showing microscopic evidence of Kaposi's sarcoma erroneously diagnosed as Hodgkin s disease and unaccompanied by cutaneous infiltrations

Involvement of the lymph nodes in Kaposi's sarcoma has been erroneously considered to occur late in the course of the *disease* or when the tumors were

* In collaboration with Jeff Davis.

complicated by ulceration or secondary infection In Paolini's case clinical symptoms of gastrointestinal disturbances appeared long before any evidence of cutaneous changes occurred On postmortem examination numerous nodules of Kaposi's sarcoma were found in the large and small bowel, thus accounting for the early symptoms referable to the gastrointestinal tract In our second patient the involvement by Kaposi's sarcoma was limited to a single cutaneous manifestation of the disease

There seems to be no set pattern in which the lymphoma or leukemia and Kaposi's sarcoma occur One may precede the other or be found occurring simultaneously Generalized involvement of the lymph nodes by both disease processes has been studied and such studies reveal that certain nodes may present the pathologic picture of one of the lymphomas, and others may show histopathologic findings characteristic of Kaposi's sarcoma In Sach's and Gray's case a biopsy from the involved skin of the foot showed lymphatic leukemic infiltration in the deeper portion of the cutis and Kaposi's sarcoma in the middle and upper layers of the cutis in the same biopsy specimen

There is now general agreement by physicians who have observed the clinicopathologic phenomena of these two disease processes present in one individual that it is not just happenstance but that there is some related or common causal factor This point gains emphasis when one considers that both lymphoblastoma and Kaposi's sarcoma arise in cells of the same mesenchymal origin

Further supports of the similar pathogenesis of the two neoplastic diseases are the known hematologic changes and involvement of the lymphatic system that are present in many patients with Kaposi's sarcoma Although there are not consistently important changes in the total white count and differential leukocyte count, monocytosis and less frequently eosinophilia are pointed out as striking by Dorffel The mononuclear cell count may be as high as from 22 to 28 per cent These same factors are also of significance in favor of those who adhere to the reticuloendothelial origin of Kaposi's disease as proposed by Dorffel, Choisser and Ramsey, and more recently by Tedeschi

When two neoplastic diseases coexist, each having such a guarded prognosis, one would expect the period of survival to be considerably shorter than in a patient having only one of these diseases Yet interestingly enough, the period of survival of one of these patients (case report No 46) was ten years This is above the average rate of survival for a large group of cases having only Kaposi's hemorrhagic sarcoma In McCarthy and Pack's series of 36 cases of Kaposi's sarcoma, the average survival interval in cases receiving treatment was eight years The patients with these two diseases presented such interesting pathologic and clinical features that each of the cases will be described in detail These cases offer valuable data regarding possible pathogenic relationship between Kaposi's hemorrhagic sarcoma and malignant lymphoma

CASE REPORT NO 45 LYMPHOSARCOMA AND KAPOSI'S HEMORRHAGIC SARCOMA

L C, a 66-year-old Russian Jew, was admitted complaining that seven weeks prior he had experienced a minor injury to the second toe of his left foot Following this injury the toe and distal portion of the foot became inflamed, bluish in color, and swollen Three weeks later the toe ulcerated, the swelling increased, and pain was severe He then consulted a dermatologist who performed a biopsy This specimen was submitted to another hospital where a microscopic diagnosis of melanocarcinoma was made The patient was then referred to us for treatment

He related a previous history of having chronic bronchitis and frequent upper respiratory infections during the past 20 to 30 years. For a corresponding time he had a bilateral inguinal lymphadenopathy For five years he had been treated for acute glaucoma.

Physical examination revealed a slightly swollen left foot on which the second toe was twice the normal size and showed a dark blue ulceration surrounded by multiple bluish papules and nodules, some of which were ulcerated. The dorsal and lateral surface of the great toe and the plantar aspect of the third toe were similarly involved in this deep-bluish discoloration and studded with a nodular infiltration A generalized lympadenopathy was present with palpable nodes in the axillary and inguinal regions bilaterally and in the upper anterior cervical chain on the right. A small lymph node was also present in the anterior axillary line at the level of the fifth rib on the right side. The results of the remainder of the physical examination were essentially normal. Laboratory findings were blood sugar 86 mg per cent blood urea nitrogen 19 mg per cent erythrocytes, 4,700 000 per cu. mm. of blood, white blood cells 6,500 (polymorphonuclear leukocytes 70 eosinophils, 2 lymphocytes 30) hematocrit, 42 per cent, and hemoglobin, 12.5 gm Urine analysis was normal. ECG and x ray of the chest were within normal limits.

A biopsy taken from the left great toe was first interpreted as possible malignant melanoma, thus agreeing with the pathologic diagnosis previously made elsewhere on tissue removed from the second toe.

The character of the generalized lymph adenopathy suggested the possibility of a coincidental lymphoma. For this reason an axillary lymph node was removed. Microscopic examination of this node showed no evidence either of metastatic melanoma or lymphoma.

A midthigh amputation was performed with a left groin dissection in continuity Microscopic examination of the groin nodes was found to be negative for malignant tumor Diagnosis of the primary tumor was Kaposi's sarcoma with multiple satellite



FIG. 289 Kaposi's hemorrhagic sarcoma and lymphosarcoma. This patient had both Kaposi's sarcoma and giant follicular lymphoma (Brill-Symmers disease) A. Clinical appearance of Kaposi's sarcoma involving the medial portion of the foot. B Gross specimen obtained from the amputated extremity (Case report No 45.)

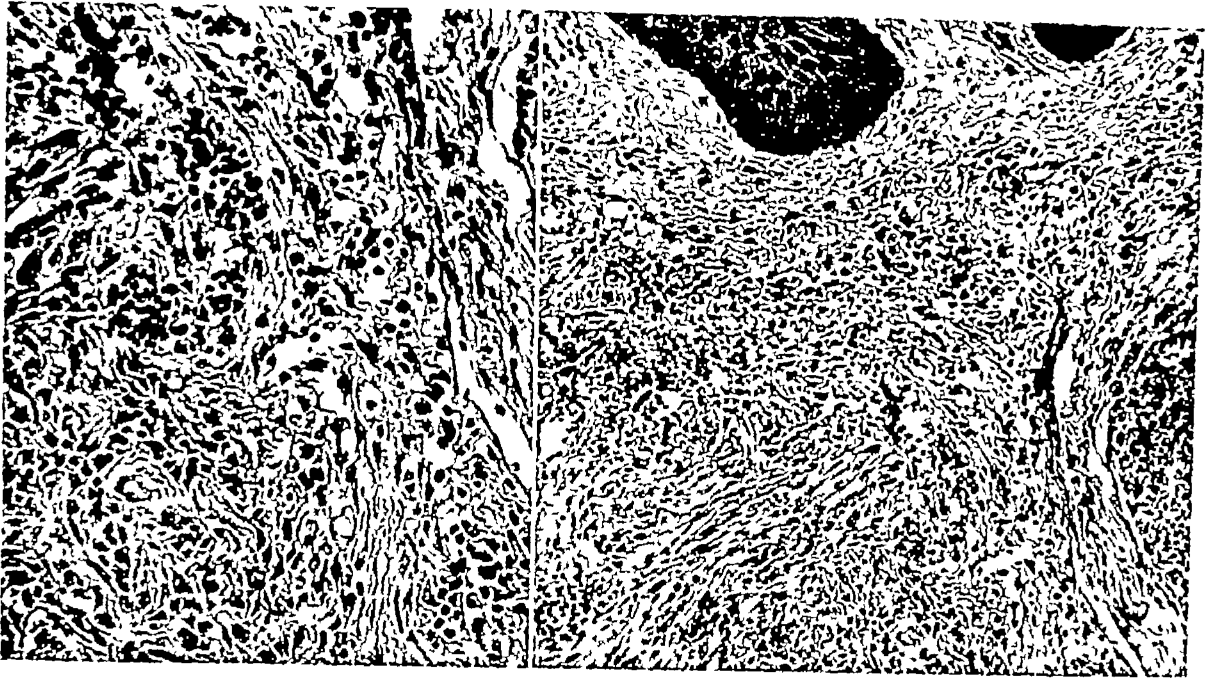


FIG 290 Kaposi's hemorrhagic sarcoma and lymphosarcoma (same patient as Fig 289). Section of skin showing Kaposi's sarcoma (*Right*) Low-power photomicrograph (*Left*) High-power magnification (Pack and Davis, A M A Arch Dermat & Syph 69 604, 1954)

nodules The previous biopsy from the toe which had been diagnosed as melanoma was then reviewed, and the diagnosis was changed from melanoma to Kaposi's disease (idiopathic hemorrhagic sarcoma)



FIG 291 Kaposi's hemorrhagic sarcoma and lymphosarcoma (same patient as Figs 289 and 290) Axillary lymph node, demonstrating characteristic giant follicular involvement of Brill-Symmers disease (Pack and Davis, A M A Arch Dermat & Syph 69 604, 1954)

The postoperative course was uneventful During the next month he suffered acutely from the phantom-leg syndrome in the amputation stump Six weeks later, bilateral inguinal lymphadenopathy appeared, this had not been present since his amputation and groin dissection

Five months later (six months after operation) the right inguinal nodes were removed for histologic examination and were diagnosed as giant follicular lymphoma (Brill-Symmers disease) X-ray therapy was then directed to a port over the right inguinal region

The pain in the amputation stump became so increasingly severe that it was necessary to perform a bilateral cordotomy for relief of the discomfort The patient died 10 months after operation and necropsy revealed (1) ectopic kidney, left, (2) bilateral pyelonephritis, (3) pleural effusions, bilateral, with atelectasis of left lower lobe of lung, and (4) pneumonia, right middle and lower lobes (Figs 289–291)

CASE REPORT NO 46
GIANT FOLLICULAR LYMPHOMA AND KAPOSI'S HEMORRHAGIC SARCOMA

S R, a 50-year-old Jewish dentist, first noticed a reddish macule on the glans penis in September, 1939 It enlarged to 1 cm

in diameter during the next two months and became verrucous in appearance, at which time it was removed with a cautery by his family physician The specimen was examined by Dr Fred W Stewart who pronounced it to be Kaposi's hemorrhagic sarcoma of the glans penis

Two months later the patient was first seen by us.

He had a history of recurrent attacks of joint pains between 1934 and 1938

Physical examination revealed a 1 cm healing defect over the posterior surface of the glans penis as a result of the recent fulguration The remainder of the physical examination was normal except for large inguinal lymph nodes that were bilaterally palpable An aspiration biopsy from the inguinal nodes was negative except for evidence of hyperplasia. Nevertheless, it was decided that a bilateral groin dissection should be performed. The microscopic examination of the operative specimen at this time was reported as showing only lymphoid hyperplasia.

The patient was thereafter examined at frequent intervals There was no further evidence of dissemination of his Kaposi's sarcoma, but in December 1944 he developed a generalized lymphadenopathy with palpable nodes bilaterally in the iliac quadrants, axillae and anterior cervical chains A biopsy of one of the lymph nodes from the neck was diagnosed as giant follicular lymphoma (Brill Symmers disease)

X ray therapy administered to these regions produced remarkable regression Repeated blood counts and urine analyses showed no abnormal changes In March, 1946 he developed a hard, firm mass in the left lower quadrant of the abdomen which was diagnosed as retroperitoneal lymphosarcoma Deep x ray therapy was then administered to this region with temporarily satisfactory regression During the next two years he developed definite splenomegaly with recurrence of the retroperitoneal lymph node enlargement as well as progression of the generalized lymphadenopathy X ray therapy was continued, but by the beginning of 1948, he was becoming progressively weaker and the discomfort more pronounced. He was continued on supportive medical care with repeated hospital admissions By the first part of 1949 he had developed mediastinal lymphadenopathy and later bloody pleural effusion He died in July 1949 of generalized lymphomatosis.

We were interested in determining in this case, if possible, just how early demonstrable pathologic changes were present that could be interpreted as evidence of lymphosarcoma. With this in mind, we requested Dr Fred W Stewart to review the operative specimen of the inguinal lymph nodes that had been removed on the patient's first hospital admission and had been reported negative at that time In the light of the subsequent clinical course of this patient, Dr Stewart kindly reviewed these microscopic specimens with the following comment

"The thing about these nodes that attracts my attention is the relatively large size of the germ centers that ordinarily would contain large reticulum cells and phagocytic elements These aren't present, however and the centers are made up of intermediate lymphocytes It is difficult to judge in retrospect but may enable us to judge other cases in the future I would say that the probability is great that disease *is* present in these nodes"

Thus Doctor Stewart's re-evaluation of this patient from the pathologic standpoint enables one to state that in this case both disease processes *i.e.*, Kaposi's sarcoma and lymphosarcoma, had been present concurrently at least since the initial onset of his symptoms ten years previous to his death.

CASE REPORT NO 47: KAPOSI'S HEMORRHAGIC SARCOMA AND MALIGNANT LYMPHOMA

R F a 75-year-old Austrian, Jewish, married woman, had been in good health until 1951 when she first noticed a dark purplish macule over the right ankle. It later ulcerated, with subsequent edema of the entire leg At the same time she noted the gradual appearance of multiple pigmented lesions over the right thigh and left leg Two months prior to her admission to the hospital new lesions had developed on the left forearm, and she experienced sharp shooting pains in the right ankle During the past several weeks the patient

complained of anorexia and loss of weight Her past history was noncontributory except that in December, 1943, she had a carcinoma of the right forearm excised.

Physical examination showed bilateral pitting edema of both lower extremities with extensive varicosities There were multiple individual and conglomerate purple cutaneous nodules and dark-red macules extending up the medial aspect of the right leg and the medial and anterior surface of the thigh The left leg was similarly involved with fewer nodules One of the larger group of nodules over the right ankle was ulcerated Several nodules were present over the posterior portion of the left forearm Tender inguinal and axillary lymph nodes were palpable bilaterally. The remainder of the examination was not remarkable The liver and spleen were not palpable X-rays of the chest, urine analysis, blood count, and differential count were all within normal limits

A diagnosis of Kaposi's sarcoma was confirmed by a biopsy of a cutaneous nodule from the right thigh Several days later a biopsy of the lymph nodes in the left axilla was diagnosed as malignant lymphoma

X-ray therapy was administered to the lesions of the skin as well as to the regional lymph nodes, with regression of the lesions

CASE REPORT NO 48
KAPOSI'S HEMORRHAGIC SARCOMA AND MALIGNANT LYMPHOMA

M R, a 24-year-old white, Italian, married woman whose previous history was irrevelant, complained that for the past two years she had noticed a pruritic macular area just inferior and lateral to the right breast During this period she felt a bit weak and had noted considerable lassitude There had been no change in weight About seven months previously she had detected swollen lymph nodes in the posterior auricular region From time to time since, she had felt enlarged lymph nodes in the axilla, neck, and groin

On physical examination a generalized lymphadenopathy was evident Enlarged lymph nodes were palpable in the posterior auricular region bilaterally, extending down both posterior cervical chains, as well as in the axillary and inguinal regions and in the supraclavicular fossae A round, hard mass suggestive of enlarged lymph nodes was palpated on the right upper outer quadrant of the right breast The skin was generally hyperpigmented Just inferior and lateral to the right breast, an extensive, scaling, darkly pigmented macular area was noted Roentgenograms of the chest were negative A blood count showed erythrocytes, 3,900,000 cu mm., white cell count, 3,900 (polymorphonuclear cells, 65, large lymphocytes, 10, small lymphocytes, 19, transitional, 4, eosinophils, 1, basophils, 1), and hemoglobin, 80 per cent

A biopsy of one of the lymph nodes was reported as "a typical picture—apparently from an outlying node with the process not fully developed Diffuse lymphocyte overgrowth with partial obliteration of landmarks and face of reticuloendothelial cells forming aggregates—suggesting possibly Hodgkin's disease or possibly tuberculosis" In view of the microscopic diagnosis and the distribution of the generalized adenopathy, a clinical diagnosis of Hodgkin's disease was made

The patient received x-ray therapy at intervals over the next three to four years During this time additional enlarged nodes appeared in the groin, and the popliteal and epitrochlear regions. They were treated by x-ray therapy with satisfactory regression

On March 4, 1937, the patient appeared pale, weak, and undernourished There were numerous moist rales in her left chest and a positive D'Espine's sign There was a generalized lymphadenopathy. The liver edge was palpable two finger-breadths below the costal margin The spleen was not palpable. A roentgenogram of the chest was normal Red blood cells were 3,680,000 per cu mm, white blood cells, 1,600 (polymorphonuclear leukocytes, 66, large lymphocytes, 3, small lymphocytes, 23, transitional cells, 8), and hemoglobin, 70 per cent Urine analysis was normal At this examination a number of small purplish nodules suggestive of Kaposi's sarcoma were observed on the skin of the left forearm, both lower extremities, and about the ankles

Biopsies of skin nodules on the back of the left leg and right wrist and from one of the lymph nodes of the neck were all diagnosed as Kaposi's sarcoma At this time

the node biopsied in 1931 was reviewed in view of the present pathologic findings and the diagnosis was revised to that of Kaposi's sarcoma. She died in August, 1937

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DISTINCTIVE BLOOD VESSEL AND LYMPHATIC NEOPLASMS

LYMPHANGIOMA AND LYMPHANGIOSARCOMA

LYMPHANGIOMA

Lymphangiomas are much less frequent than hemangiomas In numerous instances a tumor may contain an admixture of lymphangiomatous and hemangiomatous elements The lymphangiomas, although benign, possess the remarkable power of continued growth, infiltration, and progressive extension over adjacent skin throughout childhood and adolescence They are invariably of congenital origin through embryonic sequestration of lymphatic tissues but often do not make their recognizable appearance until later in infancy The condition of lymphangiectasis with edema due to lymphatic obstruction is not to be confused with lymphangioma, which is a true tumor consisting of neoplastic lymph vessels and supporting stroma Nevertheless, lymphangiectasis or chronic lymphatic obstruction should be considered in this relationship because it is sometimes the preneoplastic state resulting ultimately in lymphangiosarcoma

CLASSIFICATION

1 *The simple or papillary lymphangioma (lymphangioma circumscriptum cutis cysticum)* This tumor is composed of minute lymph cysts, conglomerate or agminated, situated superficially in the skin and subcutaneous tissues and in the mucous membrane of the oral cavity Warty excrescences on the skin and mucosa are translucent and flecked with red due to telangiectasis, they exude a sticky lymph on pressure Tiny blebs may appear on the surrounding skin at points quite remote from the body of the main tumor, this accounts for the difficult task of determining the exact peripheral limits of the lesion

2 *The cavernous lymphangioma* This tumor is usually more discrete, of greater bulk, situated subcutaneously, and compressible but not fluctuant It is supported by a vascular connective-tissue framework interspersed between the small multilocular cysts, lined by endothelium and containing lymph The superjacent skin may or may not be involved by the tiny wartlike blebs, which are pathognomonic for lymphangioma The common localizations are around the pelvic girdle and shoulder girdle, including the neck, occasionally the tongue or cheek or lip may be partially or completely replaced by this tumor

3 *The cystic hygroma* This tumor differs in no way from the preceding type except by the size of the locules and their distribution in and around deep anatomic structures Theoretically they should originate relatively earlier in the development of the embryo because of two anatomic facts the sites

of origin correspond to the locations of the primitive lymph cisterns (e g., the neck, the axilla, the groin, and the retroperitoneal iliac spaces) and furthermore, the neoplasm often incorporates the surrounding blood vessels nerves and muscles simulating an infiltration In the hygroma cysticum one often sees large collections or aggregates of lymphoid tissue some with well-developed germinal centers. These inclusions testify to the early conjoined origin of the lymphoid tissue and primitive lymph vascular systems The skin is seldom involved and moves freely over the cystic hygroma, which is fluctuant, movable, and seemingly encapsulated. The gross character of the lesion gives a false sense of ease in removal. The most common location is in the neck (hygroma cysticum colli) but instead of its confinement to this site, it may be found to extend deeply beneath the clavicle to involve the axillary and pectoral regions Aspiration with the removal of lymph is a satisfactory diagnostic test in differentiating the mass from a branchiogenic cyst.

4. *Systemic lymphangiomatosis* In our opinion these lymphangiomas which involve an entire extremity extending from the shoulder to the finger tips or from the groin to the toes probably originate with the budding of the limb early in the development of the fetus because the neoplasm is diffusely distributed throughout all the structures of arm or leg, infiltrating the muscles and intermuscular spaces, even the periosteum and bone The arm or leg may become grotesquely swollen and deformed in fact it may become an encumbrance with marked disability

TREATMENT

Cryotherapy using carbon dioxide ice, has not been worthwhile *in* the treatment of the superficial lymphangiomas. Electrodesiccation of the skin manifestations has left residual blemishes and keloids followed by early recurrence The lymphangiomas in our experience have proved to be quite radio-resistant, and therefore x ray and radium therapy are never employed. Sclerosing solutions such as sodium morrhuate or quinine and urea hydrochloride have limited use the tumors made up of innumerable tiny cysts are obviously unsuitable for such treatment because of the impossibility of injecting each cyst. Some cystic hygromas can be obliterated by the judicious use of these sclerosing agents the large cysts are evacuated, and with the needle still in place, the solution is then injected.

Surgical excision is the method preferred and is the immediate answer to the problem of the superficial and cavernous lymphangiomas which are well localized. The surgical dissection of cystic hygromas in infants may prove to be unexpectedly difficult. Every precaution should be taken to be sure the child is old and strong enough to be a good surgical risk, blood transfusion should be available and prophylactic chemotherapy instituted before the operation Before antibiotic drugs were available the operative mortality for patients with cystic hygromas was reported from several sources to be as high as from 30 to 40 per cent. The locules of the hygroma occur so deeply in the tissues and are so intermingled with important structures that the dissection must be cautious meticulous, and thorough. Before the period of antibiotic therapy an incomplete excision of a lymphangioma was most hazardous and several of our young patients almost lost their lives from fulminating infections, usually streptococcic. These infectious episodes would recur intermittently and without warning the lymph locules would harbor these germs sometimes for months Now with the protection afforded through the prophylactic use of antibiotics we sometimes do segmental ex

cision of the large lymphangiomas in multiple stages In the case of the systemic lymphangiomas, the segmental excisions may be in the form of Kondoléon operations on the arms and legs in order to overcome the disability and monstrous disfigurement of the elephantiasis resulting from this tumor

Congenital Lymphangiectasis (Lymphedema) of Milroy

Doctor W F Milroy described a family of six generations, comprising 97 individuals, in which, of 22 members with congenital lymphedema, or about 23 per cent of the whole number, 12 were males, 7 females, and 3 of unknown sex This appears to show that the deformity is more common among the males of a family. The invariable characteristics of the disorder have been. congenital origin with steady growth corresponding to the normal growth of the body until adult size is obtained, the limitation of edema to one or both lower extremities, the area involved varying, permanency of the edema, and entire absence of constitutional symptoms or local symptoms aside from those described

A significant finding was that one patient in the third generation was born with an enlarged foot that showed no changes whatsoever until the age of 20 when she was thrown from a carriage and sustained an injury to the sound leg The immediate effects of the injury passed away in a short time, but from this date on, the leg began to enlarge and continued to do so until it attained enormous size However, at the same time it in no way interfered with the health or activity of the individual In a second patient of the third generation, who was normal at birth and did not show any change in her extremities until she was 12, one ankle developed the appearance of having been sprained, with pain, swelling, and tenderness being apparent and without history of trauma All symptoms subsided with the exception of the swelling, and this increased until it involved the entire foot and leg In Osler's patient bearing this affliction, there was involvement of various regions including the hands, fingers, kneecaps, and buttocks

Mason and Allen state that there are two types of lymphedema, simple and familial Simple congenital lymphedema affects individual persons in a family Familial congenital lymphedema affects a sufficient number of blood relatives to indicate that a disturbance in the genes is responsible This condition, which is known as Milroy's disease after the original description by Milroy, is a clinical syndrome which we have never observed We doubt if this syndrome has been observed by many other authors who have described cases with such designation Allen himself feels the term should be reserved for lymphedema which is both congenital and familial These authors present five cases of congenital lymphedema observed at the Mayo Clinic, in an attempt to clarify the clinical and pathologic characteristics of this disease They give a good description of clinical characteristics as well as differential diagnosis The pathologic study of skin, deep fascia, and intervening structures is an excellent description, but it appears that there is no comment concerning involvement of the musculature itself, and nothing of significance was found in either the blood vessels or the nerves

Comment is made that congenital lymphedema, to be sure, is characterized by the replacement of normal subcutaneous fat with widely dilated lymphatic spaces and with fibrous tissue, but the cause of the changes is obscure It is probable that the original abnormality is the increased surface area which is occupied by lymphatic vessels Such a change would produce stasis of lymph which may cause fibrosis, as

lymph is an excellent culture medium for the growth of fibroblasts What causes the lymphangiectasis? It may be viewed as a developmental anomaly which raises the same questions about origin as with other kinds of developmental anomalies. It seems certain that congenital lymphedema is not simply a condition which develops during intra uterine life and which can be compared with lymphedema that begins at the age of 3 Microscopic studies indicate the tissue in the two types differs morphologically

Chronic obstructive lymphedema of upper and lower extremities, due to radical extirpation of axillary and inguinal lymph nodes, respectively or due to infectious, parasitic, or neoplastic diseases which occlude the lymphatics at these junctions, is a common state The role of such lymphangiectasis in the subsequent development of malignant lymphangiomatous tumors will be discussed later

CASE REPORT NO 49: LYMPHANGIOMA OF THIGH

W K., a 12 year-old boy presented a large subcutaneous tumor which measured 12 cm. in diameter and was situated over the anterior surface of the left thigh. Several telangiectatic and lymphangiectatic vesicles were present in the superjacent skin. The tumor had been detected at birth It was excised at another institution but recurred within six months After preliminary low voltage x ray therapy a radical dissection of the tumor was done in 1934. When the patient was last examined in 1945 there was no evidence of recurrence and the leg was perfectly functional.

CASE REPORT NO 50: CYSTIC LYMPHANGIOMA (HYGROMA) OF GROIN

L. W., a 15-year-old boy had a lobulated, soft rounded, purplish, compressible, semicystic, subcutaneous tumor measuring 20 cm. in diameter and situated in the right groin. It was first observed when the patient was 3 months of age it slowly increased in size until adolescence when it grew *rapidly following vigorous exercise* playing basketball. Injections of sodium morrhuate were attempted, with partial success. Radical surgical dissection was done but the tumor was so closely adherent to the corium that the thin skin flaps did not survive Skin grafting was subsequently done. There was no recurrence ten years later (Fig 293)

CASE REPORT NO 51: CONGENITAL LYMPHANGIOMATOSIS

N W a 3-year-old child, presented a massive overgrowth of the buttocks and

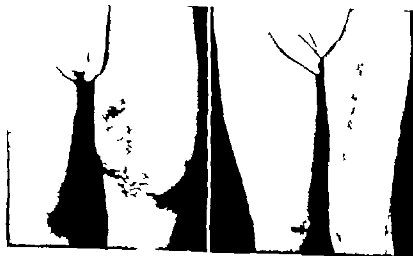


FIG. 292. (*Left*) Congenital hemangiolymphangioma of thigh. (*Right*) Photograph taken 9 years after irradiation and surgical excision. (Case report No 49)



FIG 293 Cystic lymphangioma (hygroma) of groin *A* Preoperative appearance *B* Postoperative appearance *C* Gross specimen This patient has remained free of neoplasm for 10 years (Case report No 50)

scrotum at birth The masses consisted of congenital lymphangiomatosis and increased in size with the development of the child until they reached the proportions shown in Figure 296 The scrotum was involved by what was practically a cystic hygroma Rectal examination was normal, suggesting that the tumor was limited to the regions indicated in the figure It had been planned to perform surgical resection in possibly three stages, but the parents refused treatment

CASE REPORT NO 52
CAVERNOUS LYMPHANGIOMATOSIS AND HEMANGIOMATOSIS

The patient, a 5½-year-old lad, was delivered per vaginam, although his mother was in labor for 36 hours, presumably because enlargement of the infant's head necessitated the use of forceps At birth an enormously developed left arm, left side of the thorax, neck, face, and left side of the tongue were observed He had considerable



FIG 294. Superficial lymphangiomatosis of groin. *A*. Recurrence 3 years after local excision. Note the characteristic tiny vesicular blebs. *B* Patient remains cured, 5 years after dissection and skin-grafting

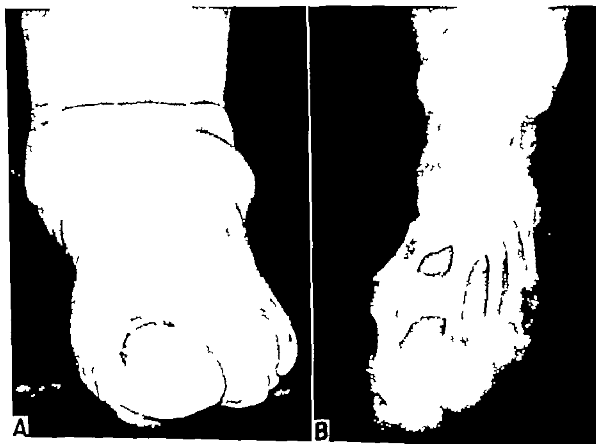


FIG. 295 Clinical appearance of a congenital massive lymphangioma in an adult, producing a "pied bot." The bone absorption, sclerosis, fusion, and obliteration of joints are a consequence of lymphangiomatous infiltration of the entire foot.

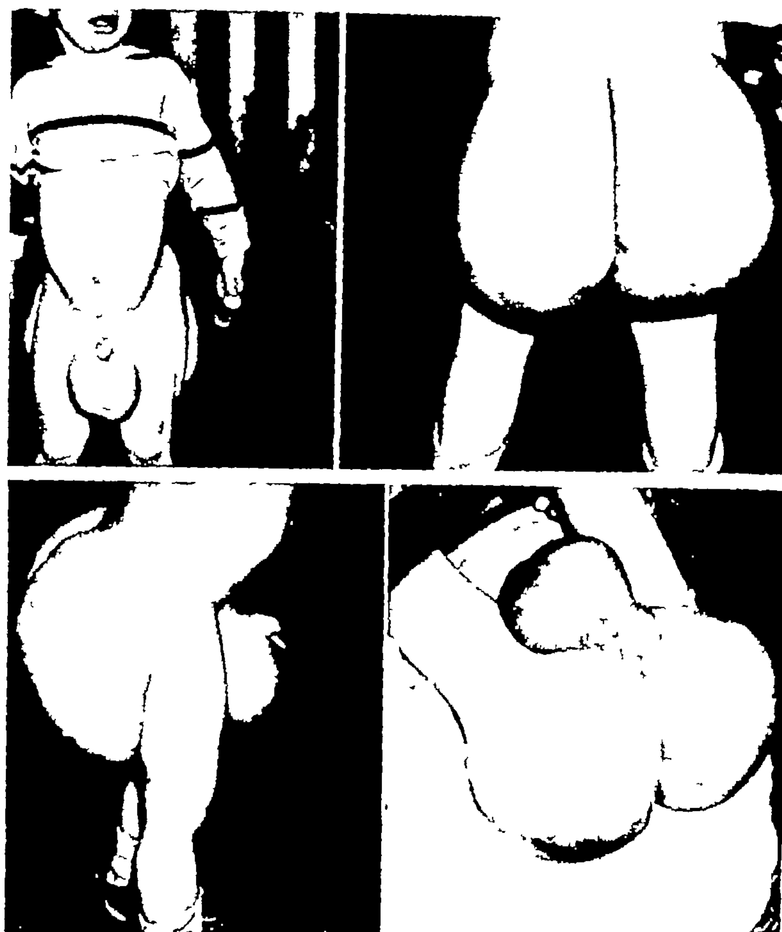


FIG 296 Huge congenital lymphangioma involving the scrotum and buttocks (Case report No 51)

respiratory difficulty, presumably due to sublingual swellings A diagnosis of extensive cavernous lymphangiomatosis and hemangiomatosis was established The child received numerous forms of treatment by various physicians consulted by his parents He was first treated by x-ray therapy in Texas, this was followed by a series of injections of sclerosing solutions at the Presbyterian Hospital in New York When, at the age of 5½, the patient was seen by us, the growth of the systemic lymphangioma had accompanied his normal growth pattern The measurements of the arms, 10 cm inferior to the tip of the acromium process, revealed the left arm to be 21 cm in diameter and the right to be 15 cm At 24 cm from the tip of the acromium process, the left forearm measured 29 cm and the right 15 cm in diameter Roentgenograms of the chest and skull were normal, revealing no bony overgrowth A successful resection of the lymphangioma of the neck was accomplished It had been planned to perform a modified Kondoléon operation to attempt to correct the arm deformity, but the patient moved to a distant community where a local physician performed an exploratory incision into the lymphangiomatous arm, this resulted in a severe erysipeloid infection so common after incisions directly into this form of neoplasm It is believed that this child will be forced to suffer an amputation of the left upper extremity (Fig 297)

LYMPHANGIOSARCOMA

LYMPHANGIOSARCOMA IN ELEPHANTIASIS CHIRURGICA

Stewart and Treves described an unusual tumor entity which develops in an edematous upper extremity following radical mastectomy long after the breast cancer has apparently been controlled The neoplasm is a lymphangiosarcoma of diffuse and multicentric origin, its earlier recognition in the past has been handicapped presumably by the error

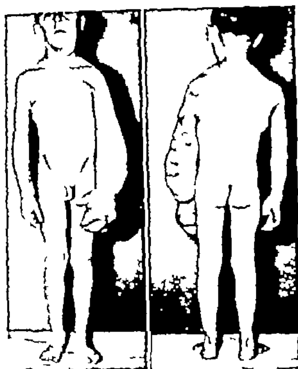


FIG. 297 Enormous lymphangioma, with hemangiomatous involvement of the upper left portion of the body (*Left*) Anterior view Note involvement of neck, cheek, and mouth. (*Right*) Posterior view (Case report No. 52.)

of considering the lesion as recurrent in operable mammary cancer The arm which becomes the site of this tumorigenesis is tremendously swollen and hypertrophied, with brawny atrophic, hyperkeratotic, suffused, purplish skin, and is attended by limitation in function, pain, and occasional attacks of erysipeloid infection

After an interval of several years (6 years in Treves's patients and 10 years in Pack's case) a purplish, elevated nodule or macule appears in the skin of the arm Numerous other lesions develop and may become confluent red, papillary and ulcerated. The skin of the entire arm and hand may ultimately become involved. The tumors bear no resemblance to the cutaneous nodules of recurrent breast cancer Death is usually due to pulmonary metastases

The histologic details of the tumor have been thus described by Fred W Stewart In the early stages of growth its origin is in dilated lymphatic vessels occurring outside small venous channels or in the subcutaneous tissue not definitely associated with venules In relation to larger veins, the solid tumor apparently originates from the lymphatics surrounding the vein and actually within the vein wall tumor emboli have been demonstrated Stewart has demonstrated every transition from the stage in which the tumor cells still line channels up to the diffuse or solid tumor growth Fibrinous edema occurs throughout the subcutaneous tissue, and there is infiltration of plasma cells and lymphocytes, which may in some regions be closely packed and form germinal centers such as are known to occur in hygroma cysticum

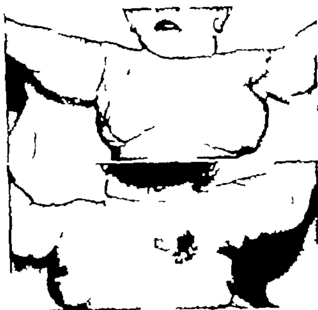


FIG 298 Congenital cystic hygromas of neck, axillae arms and scapular regions. Removed in serial operations.

Stewart and Treves are unwilling to consider the lymphedema alone as the predisposing factor because these lymphangiosarcomas have not been reported as sequential to other diseases associated with chronic lymphedema such as filariasis However it is our opinion that case reports of this tumor s developing in a lymphedematous lower extremity following filariasis or radical groin dissection will ultimately appear and we believe the lymph stasis to be an etiologic factor Kaposi's sarcoma, which occurs usually on the lower extremities, is almost always associated with, and preceded by vascular disturbances In

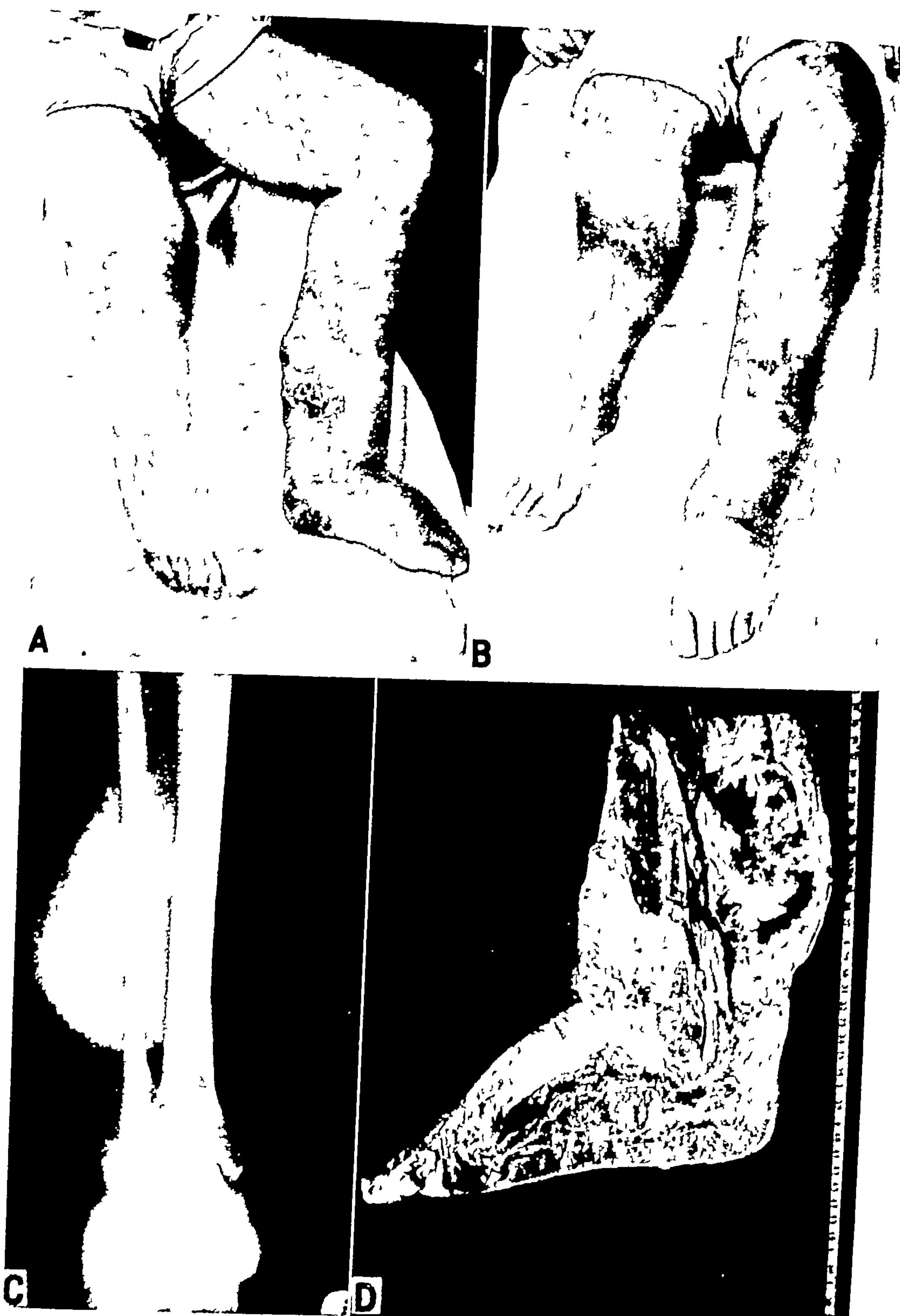


FIG 299 Development of lymphangiosarcoma in leg containing congenital lymphangiomatosis *A*, *B* Note the lymphangiectatic hyperkeratoses on medial aspect of left heel and between toes of left foot Right leg is congenitally deformed, thus exaggerating the elephantiasis and overgrowth of long bones of the left lower leg This phenomenon occurs occasionally with diffuse angiomatosis of an extremity An ulcerating lymphangiosarcoma developed on the medial aspect of the left ankle *C* Roentgenogram showing the appearance of the lymphangiosarcoma *D* Hemisection of amputated leg illustrating the extent of the lymphangiosarcoma



FIG. 300 Lymphangiosarcoma in elephantiasis chirurgica, occurring 12 years after radical mastectomy

fact we believe lymphangiosarcoma in elephantiasis chirurgica and Kaposi's hemorrhagic angiosarcoma to be the same disease entity Lymphangiosarcoma of similar histologic structure as that observed in elephantiasis chirurgica occurs not infrequently in patients with chronic lymphedema from any cause.

CASE REPORT NO 53: LYMPHANGIOSARCOMA IN ELEPHANTIASIS CHIRURGICA

E. R discovered a tumor in her left breast 10 years before when she was 59 years old. She had nursed her three children Menopause had occurred at age 47 years A radical mastectomy had been done. The pathologist's report was "infiltrating duct carcinoma Grade III No evidence of metastases in axillary nodes"

Present Illness

She was first seen by us at the age of 69 years. There was no evidence of recurrence in the scar and no enlargement of supraclavicular lymph nodes. The entire left arm was livid, markedly swollen and lymphedematous from wrist to shoulder Innumerable firm tender bluish purple nodules were scattered throughout the skin of the forearm and elbow these were from 3 mm. to 1 cm in diameter (Fig. 300)

Treatment

An interscapulothoracic amputation was done on September 17 1947 The postoperative convalescence was normal. The report of the pathologist was lymphangiosarcoma. She remained asymptomatic for two years and then developed recurrent lymphangiosarcomatosis and died February 12, 1950

Comment

The swollen arm had developed immediately after the radical mastectomy A biopsy taken before the interscapulothoracic amputation revealed that the skin nodules were not recurrent mammary cancer

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HEMANGIOPERICYTOMA

DEFINITION AND GENESIS

Arthur Purdy Stout and Margaret Murray, employing the medium of tissue culture, were able to demonstrate that the epithelioid cell of the glomus tumor is derived from Zimmerman's pericyte The pericytes are presumed to be smooth-muscle cells, lacking in myofibrils but with unusual contractile qualities, whose processes surround capillaries and by contraction and relaxation change the caliber of the lumina and thus influence the rate of blood flow through this particular capillary bed

Stout and Murray originally reported 9 cases Stout later collected 25 additional cases of tumors originating from pericytes other than the glomus tumor, which is a specialized subvariant form, and designated these tumors as hemangiopericytomas It would be proper to apply the eponym *Stout's tumor* to this curious neoplasm

Many histologists have independently demonstrated the existence of the branched cells attached to the outer endothelial wall of numerous capillaries These apparent muscle cells were first noticed by Rouget in 1873, while studying the hyaloid membrane of the cat's eye They are best studied in living tissues, especially the thin membranes of amphibians, such as the tongue and web of frogs, the tail of tadpoles, and the nictitating membrane

The appearance of the cells varies *depending on the state of contraction* or relaxation of the capillaries. These cells on the outside of the endothelium possess an ovoid nucleus and two or more primary protoplasmic processes which extend along the length of the tiny vascular tube, giving off hooplike twigs which surround the vessel. When the capillary is dilated, these cells are so attenuated as to be barely visible, but when the capillary is contracted, the Rouget cells stand out as knobby protuberances on the endothelial tube August Krogh, in his classic study on capillaries, observed how changes in the *width of living capillaries were correlated* with the appearance of the Rouget cells The contraction originates at a point at which a Rouget cell is attached and spreads along the capillary When the capillary is completely contracted, the Rouget cell becomes globular and the protoplasmic processes are sharply defined. It has been generally accepted that these contractile Rouget cells are primitive smooth-muscle cells Vital staining with Janus green B has shown the presence of myofibrils in the Rouget capillary cells and in the fusiform muscle cells of the arterioles

The Swiss histologist Zimmerman in 1923 studied the branched pericapillary cells termed *pericytes* in several classes of vertebrates Using the rather capricious Golgi *silver impregnation on fixed tissues* Zimmerman also described the arrangement and morphology of the pericytes corresponding to the previ*ously discovered cells* of Rouget, and concluded that they were of smooth muscle origin

Aschoff and Marchand contradict the theory of the smooth-muscle origin of the Rouget cells they grouped all cells outside the endothelium of the capillary into an indiscriminate group of "pericytes" The selective vital staining of myofibrils in the Rouget pericytes by the use of Janus green B would seem to prove the muscular nature of these cells In one key case they were able to trace this relationship of smooth muscle cell and pericyte from the common rounded pericyte to the differentiated muscle cell containing recognizable *myofibrils*

PATHOLOGIC ANATOMY

Stout has described the tumor thus "These were all vascular tumors featured by a proliferation of capillaries surrounding these were massed spindle-shaped or rounded cells somewhat in the fashion of the vessels and cells of the glomus tumors but without the *highly organoid architecture and en*capsulation of that spectacular neoplasm or the remarkable number of nerves and the paroxysmal attacks of pain associated with it." One relationship that is said to be constantly found is the proliferative obvious or occult capillaries their connective-tissue sheath and outside of this the characteristic cells peculiar to the tumor Hematoxylin and eosin stain is inferior to the silver connective-tissue fiber stain, because the latter principle blackens the sheath and demon

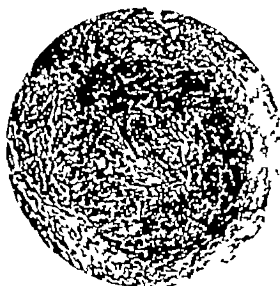


FIG. 301 A very small, limited hemangiopericytoma which shows a minute central vessel with a hyperplastic endothelium and a thick and hyalinizing wall fairly well vascularized by minute vessels.

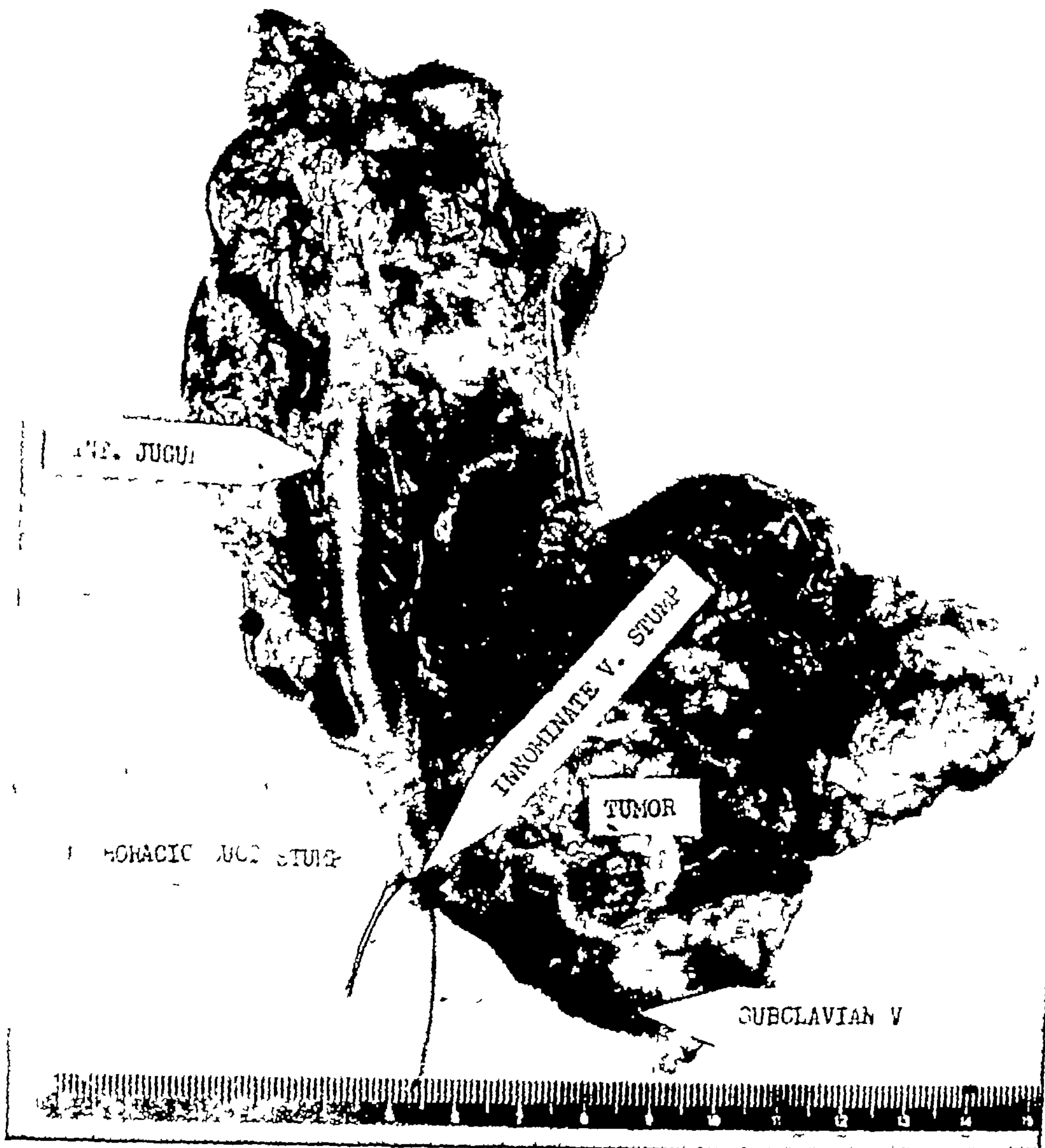


FIG 302 Hemangiopericytoma Gross specimen following radical surgical extirpation of a massive hemangiopericytoma involving the upper chest and cervical regions in a 40-year-old female (*Courtesy*, Dr Lemuel Bowden)

strates the extravaginal position of the tumor cells without the sheath By this means the neoplasms cannot be confused with hemangioendotheliomas, in which the cells are located in an intravaginal position

There are no gross features of the tumor in situ which are of diagnostic importance On casual inspection one would not necessarily suspect the neoplasm to be of vascular origin, as it is not red and the small channels do not necessarily contain erythrocytes The tumor appears clinically encapsulated, necrosis is usually absent, but an occasional tumor will contain calcified foci Stout has observed these tumors to occur congenitally as well as postnatally They may originate anywhere within the body, but the majority are found in the superficial soft tissues where they appear as circumscribed, nodular, and sometimes vascular growths Other locations include the head, neck, retroperitoneal, omental, and mesenteric tissues, orbit, tongue, pericardium, diaphragm, ileum, and meninges

The size of the tumor varies with its growth potentialities, and whereas most are small, in eleven of Stout's series the tumors exceeded 8 cm in diameter

MALIGNANT HEMANGIOPERICYTOMA

This tumor is similar to its benign counterpart but is listed here because

of 32 cases recorded by Stout which gave evidence of its malignant nature because of invasive growth properties and the development of metastases in about half of the group Sufficient data have not been assembled to permit statistical evaluation as to the proper mode of therapy but judging from the limited data on hand, it would appear that radical surgical resection is the preferred method of treatment.

Stout has commented on the large size of the malignant pericytomas and observed that they occurred in locations where complete extirpation could not be accomplished. These features coupled with the observation that none of the congenital hemangiopericytomas were malignant, suggest that the malignant variety represents a transformation from a benign hemangiopericytoma.

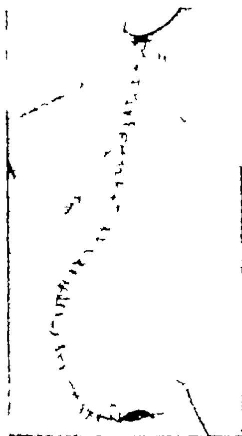


Fig 303 Hemangiopericytoma. Postoperative scar indicating the extent of the surgical procedure performed for tumor in Fig 302. (*Courtesy* Dr Lemuel Bowden.)

CASE REPORT NO 54: HEMANGIOPERICYTOMA OF VAGINA COMPLICATING PREGNANCY TWENTY TWO YEAR CURE

A 31 year-old woman, para III applied for treatment on January 26 1935 and complained of a tumor mass involving the left side of the vagina near the introitus. She had three children all born without complications In November 1934, she experienced severe vaginal pain when sitting Her last menstrual period was in October 1934. She was treated elsewhere for possible Bartholin s abscess conservative treatment was followed by incision and drainage by another surgeon No pus was encountered, but soft, greyish tumor tissue was found, first reported as a malignant angioendothelioma A therapeutic abortion was performed by the surgeon

Examination and Treatment

When examined on January 26 1935 the uterus was involuting, but the vagina was almost occluded by a fungating, vascular tumor On drainage of a complicating ischiorectal abscess, tumor tissue was found in the draining sinus. The neoplasm was inoperable therefore radiation therapy was instituted, using the following factors 180 000 volts, 0 5 mm copper and 1 mm. aluminum 50 cm T.S.D 4 pelvic ports and 1 direct perineal port, giving 300 r daily alternating until 2100 r units were given to each pelvic field, and 1500 r units to the vulvar and vaginal region. On March 1 1935 needles containing 28 6 mg of radium a total of 22 cells with 0.5 mm. platinum filter were inserted in the vagina and left in place for 102 hours and 18 minutes to give a total dose of 22 mc. destroyed, or 2928 mgh.

Course

Regression occurred slowly but completely after an intense radiation reaction. She is now living and well twenty-two years later (Fig 304)

Pathologic Report

Malignant hemangiopericytoma

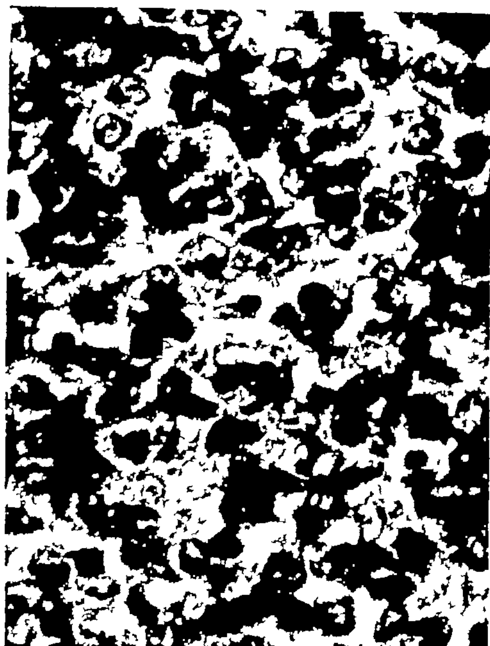


Fig 304 High-power photomicrograph of a malignant hemangiopericytoma which occurred as a huge fungating tumor in the vagina of a pregnant woman The neoplasm was cured by irradiation (a 15-year cure)

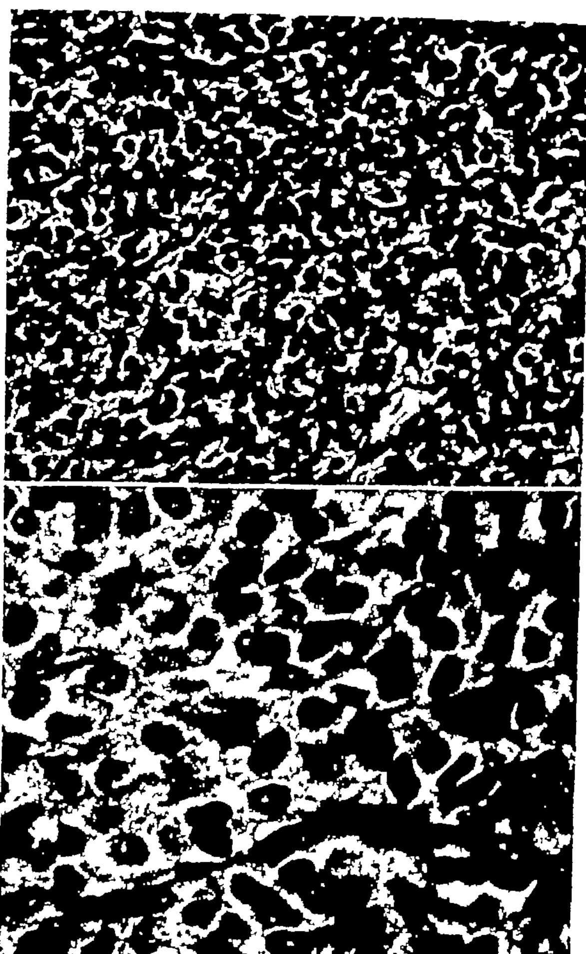


Fig 305 Low- and high-power photomicrographs of a malignant hemangiopericytoma in a 32-year-old pregnant woman

CASE REPORT NO 55 RETROPERITONEAL HEMANGIOPERICYTOMA

A 32-year-old white female developed a right retroperitoneal tumor during pregnancy This was resected, and the tumor was considered to be of low-grade malignancy The patient was delivered by Cesarean section at seven months because of placenta previa, and at this time careful exploration revealed no evidence of recurrence Four months following delivery there was evidence of involvement of the cauda equina, the patient was operated on by Dr Norman Treves, and a recurrent tumor of the right lumbar gutter and upper pelvis was removed The tissue report at Memorial Hospital was "Stout's hemangiopericytoma" Pulmonary metastases were noted prior to this second operation Neurologic signs and symptoms involving the right leg and eventually the bladder progressed Terminally the patient developed evidence of meningitis and expired six years and two months following the discovery of the original tumor mass (Fig 305)

Autopsy revealed a recurrent retroperitoneal hemangiopericytoma (Stout's tumor) with direct invasion through the fourth and fifth lumbar vertebrae into the cauda equina and subsequent purulent meningitis Numerous bulky pulmonary metastases were present

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HEMANGIOENDOTHELIOMA

DEFINITION

The most abused and confused term in the category of vascular tumors is *hemangioendothelioma*. It was coined by Frank B Mallory in 1908 and referred to a malignant tumor of blood vessel origin in which the dominant cell was endothelial. It has been unwisely used as a designation for certain benign cellular hemangiomas pathologists have not been sufficiently critical in this appellation We have had several children as patients for whom amputation of an extremity had been contemplated by surgeons, based on a classification of the tumor as hemangioendothelioma by a pathologist who was confused by the aggressive expansion and cellular character of a benign hemangioma. This is the time and place to condemn the solecism *benign metastasizing hemangioma* Certain metastasizing angiosarcomas just as some thyroid carcinomas are capable of such differentiation in their metastatic growths as to simulate benignancy

The angioendotheliomas are usually anaplastic, highly malignant sarcomas which metastasize commonly by blood vessels to lungs and other viscera, they also spread through lymphatics to regional lymph nodes Because of this tendency for lymph borne metastases the scope of surgical treatment should include these regional lymph nodes and the intervening lymphatics if at all feasible.

They are extremely vascular and fragile with known tendencies for spontaneous intratumoral hemorrhages and alarming fungation and bleeding if the lesion ulcerates through the overlying skin. In infants and children the tumor may be slightly less malignant and of slower growth but is still fatal.

HISTOGENESIS

Arthur Purdy Stout has done much to clarify our knowledge of the histogenesis of this tumor By employing a silver reticulin stain he has observed that the vascular tubes stand out in bold relief

with a distinctive pattern. Stout has defined the two criteria of hemangioendothelioma which should be uniformly present in order to establish this specific diagnosis: "First, the formation of atypical endothelial cells in greater numbers than are required to line the vessels with a simple endothelial membrane, and second, the formation of vascular tubes with a delicate framework of reticulin fibers and a marked tendency for their lumens to anastomose." The individual endothelial cells may appear polygonal, round, or even fusiform and may be grouped in continuous sheets or solid cords within and without the lumina. Tissue culture aids to identify the cell type.

PROGNOSIS

The prognosis is not good. Statistical studies are infrequent because of the rarity of the neoplasm and because many of the cases are lost among the greater group of unclassified angiosarcomas. The better term would be *angioendothelioma* rather than *hemangioendothelioma,* as we have had several patients with malignant endotheliomas originating in congenital lymphangiomas. Two such case reports are presented.

Before September, 1951, Stout recorded a total of 34 patients with malignant hemangioendothelioma. Fifteen of these occurred in the soft somatic tissues, and 19 occurred elsewhere as follows: liver, 1, spleen, 4, breast, 4, bone, 4, and 1 each in the uterus, pharynx, pleura, corpora cavernosa, penis, and sciatic nerve.

It is not surprising that metastases occur by way of the blood stream as these tumors of endothelial origin, arising within blood vessels, are more or less bathed by the blood.

Because of the difficulty in distinguishing between lymphangioendothelioma and hemangioendothelioma, both will be presented in the following case reports.

CASE REPORT NO. 56. MALIGNANT LYMPHANGIOENDOTHELIOMA DEVELOPING IN BENIGN LYMPHANGIOMA

The patient, a 48-year-old man, had congenital lymphangioma of his left leg with shortening, deformity, and marked disability of both legs. The right lower extremity was much shorter than the left, but the left was involved by a diffuse lymphangiomatous process. Fifteen years before the first examination in 1921, he detected a discrete lump developing in the medial aspect of the left leg above the ankle. It was excised elsewhere and recurred eight years later, to be re-excised, after which a free interval of two and a half years elapsed. On examination on March 30, 1936, the entire left lower leg, beginning from a point just above the tibial tubercle, was swollen, tense, and edematous. The skin was thin and atrophic with rhagadiform ulcers over the ankle. On the medial aspect of the heel was a sessile papillary growth typical of hypertrophic lymphangioma. There were similar small vesicular nodules distributed in a linear fashion in the skin on the dorsum of the toes. In the center of the scar in the mesial aspect of the leg posteriorly, there was a bluish-red, ulcerating, fungating tumor. It was extremely painful, and the patient was almost completely disabled.

The previous tumors excised were fibrous lymphangiomas. A roentgenogram of the chest revealed no evidence of pulmonary metastasis. X-ray studies of the left leg showed definite bridging of the fibula to the tibia above the lateral malleolus.

Treatment

Because of the fungation of the tumor, an amputation of the left leg just below the knee was performed. The gross specimen revealed a hard, vesiculated, hemorrhagic tumor, well circumscribed, measuring 12 × 9 × 9 *cm.*, involving the subcutaneous tissues, and infiltrating throughout the tendons and muscles of the leg. The cortex of the fibula was roughened. Microscopically, the entire leg was found to be involved by diffuse lymphangiomatosis with a localized, highly malignant lymphangioendothelioma. The patient died on the



FIG. 306. (*Left*) Malignant lymphangioendothelioma of leg developing in congenital lymphangioma in adult life. (*Right*) Benign congenital lymphangioma of the leg in same patient. Normal lymphoid aggregates. (Case report No. 56)

eleventh postoperative day of pulmonary embolism (Fig 306)

CASE REPORT NO 57: MALIGNANT ANGIOENDOTHELIOMA DEVELOPING ON A CONGENITAL LYMPHANGIOMA

A 33-year-old single woman applied for treatment on February 13 1935 Since birth she had had a congenital vesicular reddish mark on the right lateral thigh half way beneath the knee and hip It was 3 cm in diameter When 15 years of age she received radium treatment elsewhere without response It remained unchanged until 1932 then, when the patient was 30 years old, it began to enlarge until it was 5 cm in all spherical diameters. It was treated elsewhere by endothermic excision which was followed by radium and x ray therapy but recurrence developed within five months in the form of numerous hard red nodules which increased in size and spread centrifugally over the thigh

Examination and Treatment

On the initial examination the scar was surrounded by brawny induration and intradermal and subcutaneous nodules extending beneath the normal skin for a distance of 10 cm beyond the scar These nodules were exquisitely sensitive on palpation. There was one firm lymph node in the lateral inguinal group The gross appearance of the contiguous skin resembled typical lymphangiomatosis. A biopsy of the

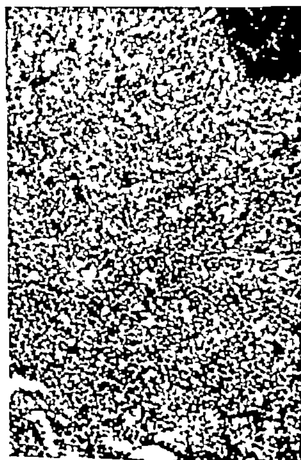


FIG. 307 Metastatic lymphangioendothelioma in a lymph node, from a malignant lymphangioendothelioma of the thigh which developed in a congenital lymphangioma. (Case report No. 57)



FIG 308 (*Left*) Hemangioendothelioma of left tibia (*Right*) The tumor of left figure after treatment by curettage and irradiation Four years later a similar tumor of the left patella was excised The patient is well 5 years after the removal of the patellar hemangioendothelioma

nodule was reported as angioendothelioma (Fig 307) A huge excision was made of the skin, subcutaneous tissues, and fascia from the anterolateral aspect of the thigh, and a skin graft was applied The lymph node in the groin, on aspiration, contained metastatic angioendothelioma, therefore a radical inguinal and femoral node dissection was performed These nodes contained metastatic endothelioma

Before the wound had completely healed, there was definite recurrence along the upper posterolateral margin of the thigh wound High-voltage x-ray treatment was given with some satisfactory regression The patient was also treated with a 4 gm radium-element pack at a 10 cm radium distance, using 4000 mgh daily for a total dose of 60,000 mgh to the recurrence on the leg

Nine months after the operation, numerous recurrent tumor nodules from 0 5 to 2 cm in diameter developed in the skin and involved the upper inner aspect of the right thigh A roentgenogram of the right elbow revealed metastasis to bone, with destruction The patient experienced intense pain in the region of the right hip, due to the locally recurrent cancer In June, 1936, there was evidence of osseous metastases involving the humerus, femur, and vertebral column She had a constant fever of 102° There was also evidence of the involvement of her liver Death occurred one and a half years after operation



FIG 309 Hemangioendothelioma (same patient as Fig 308) Illustrating the lack of deformity following surgical treatment of a tibial (1917) and patellar (1951) hemangioendothelioma plus postoperative irradiation

Pathologic Report

Angioendothelioma, very similar in structure to Kaposi's hemorrhagic sarcoma

Comment

This case represents an unusual instance of malignant angioendothelioma developing on the basis of a preexisting benign or congenital hemangiolymphangioma

BENIGN HEMANGIOENDOTHELIOMA

In children certain capillary hemangiomas will develop a duplication of the capillary endothelial cells These are designated *hemangioendothelioma* but because most hemangioendotheliomas are malignant, it is essential to stress that this neoplasm occurring in a child is termed a *benign* or *infantile hemangioendothelioma* They tend to be superficial and limited to the skin of children while the malignant variety occurs in deeper structures, usually in older people. In this respect the hemangioendothelioma may be similar to melanomas in which the malignancy of the tumor very rarely occurs in the preadolescent person.

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GRANULATION CELL SARCOMA

Granulation-cell sarcoma is what the term implies, an acute wound sarcoma made up of neoplastic granulation tissue. The greater incidence of these tumors in childhood and infancy is probably related to the exuberance of the healing process in youthful subjects The benign analog of this tumor is the common pyogenic granuloma. The granulation-cell sarcoma may develop in an open wound in which the continuity of the skin is interrupted, even though it may be merely a puncture. Or the granulation-cell sarcoma may develop in a subcutaneous wound or bruise in a deeper injury even though the overlying skin is intact. Hence, the tumor may be readily visible or concealed in its incipiency

GENESIS

The mechanism of production of these malignant tumors is probably similar to that which obtains for the pyogenic granuloma New fibroblasts and endothelial buds grow in profusion across

the wound defect at a rate much faster than the epidermis, with a resultant excess of granulations or so-called proud flesh The tendency for excess growth is greater when restricted by overlying tissues, for example, witness the frequency of pyogenic granulomas springing from the nail bed or along the nail sulcus

The transitional phases from infectious granuloma to malignant granulation-cell sarcoma are not well known The extreme rarity of acute wound sarcoma in the face of millions of wounds sustained annually in the country gives one indication of the infrequency of this complication In the concealed origin of a granulation-cell sarcoma in a deep hematoma, the process is again a peculiar transformation of reparative healing to true neoplasia Under such conditions infection plays no part in stimulating cell growth, such as it possibly does in the open-wound variety These deep hematomas presumably call forth or excite the proliferation of fibroblasts and endothelium in an attempt to organize the blood clots When this organization is rapid and occurs under pressure—especially when the hematoma is beneath the fascia—the response exceeds the need for repair, and a true sarcoma has been known to result

DIAGNOSIS

The open granulation-cell sarcomas resemble the infectious granulomas in appearance They are red, friable, soft, extremely vascular tumors which may be the source of alarming hemorrhages from insignificant injuries The deeper or concealed tumors, covered by intact skin, are probably never diagnosed correctly in their early stages They are of soft, spongy structure, and the overlying skin may exhibit the late color changes of a bruise On palpation a sensation of fluctuation may be elicited The diagnosis is usually unresolved hematoma Fundamentally, the tumor is a subvariety of angiosarcoma

TREATMENT

Most granulation-cell sarcomas have been curetted before the true diagnosis is established Recurrence after such a procedure is rapid and inevitable Wide surgical excision conceivably might be curative The deep or hidden granulation-cell sarcomas are incised on suspicion of being hematomas, but the surgeon recognizes the curetted tissues to be a peculiar, friable, vascular tumor. The treatment of choice is radiation therapy, either by high- or low-voltage roentgen rays (depending on the depth and degree of infiltration of the tumor) or by the application of radium plaques or trays at relatively short radium–skin distances It is seldom necessary to insert interstitial radon for supplementary irradiation The granulation-cell sarcoma is very radiosensitive, approaching the lymphosarcoma in its rapidity of response The degree of infection of the tumor handicaps the effort toward complete sterilization, but this can be accomplished by well-planned radiation therapy The deep granulation-cell sarcomas may metastasize widely to subcutaneous tissues, pericranium, lymph nodes, lungs, liver, and bone

CASE REPORT NO. 58 GRANULATION-CELL SARCOMA IN A CHILD

D A, a girl 2½ years old, was referred for treatment in April, 1936 Five months previously she had fallen and injured her temple This injury left a large, deep hematoma which underwent the color changes of a bruise and slowly regressed by absorption As part of it remained after four months, the family physician incised and curetted the lesion under the impression that it was a hematoma The granular tissue removed was suggestive of a true neoplasm and on microscopic study proved to be a granulation-cell sarcoma The temple was

treated by fractionated doses of high-voltage roentgen rays with complete clinical regression. Six months later the tumor recurred in several regions such as the postauricular lymph nodes, the cheek, and the eyelid.

These tumors were *phenomenally radiosensitive*, disappearing within a day or two after the administration of a small dose of roentgen rays. New tumors rapidly appeared in the scalp and subcutaneous tissues of the head, neck, and trunk. In July 1937 there was evidence of mediastinal enlargement. Further radiation therapy was given and palliation continued until January 1938, at which time death occurred from generalized sarcomatosis. The diagnosis was confirmed at necropsy which revealed metastases to cervical nodes, mediastinal lymph nodes retroperitoneal lymph nodes and ribs.

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CHAPTER 20

Tumors of Synovial Tissue

INTRODUCTION

SYNOVIAL tissue holds a unique place in the structure and function of the human organism. Ontogenetically this tissue is a part of the musculoskeletal system and is thereby closely related to the structural organization of the body. Functionally it not only joins the bones together—thereby forming the tissue support and protection for the bony hinges—but also supplies a lubricant for the osseous system. In addition, it has the protective function of supplying histiocytic elements.

Synovial tissue is composed of an inner lining of polyhedral cells and an outer layer of spindle cells of fibrous tissue. The polyhedral cells produce the viscous secretion composed of hyaluronates and mucoids and also apparently function as histiocytes. This diverse structure permits a host of cellular reactions in answer to metabolic demands and accounts for certain enigmatic cytopathologic states.

The multiple functions of synovium expose it to numerous and various traumas. The tendon sheaths of the hands and feet are being constantly traumatized either grossly or in the exiguous "wear and tear" of daily activities. Synovia are further exposed to the metabolic trauma of degenerative diseases such as degenerative osteoarthritis or the lipoid disturbances of essential lipoidosis. The activity of synovia in certain inflammatory disturbances, with the production of inflammatory arthritis, is well known.

This combination of physical trauma, metabolic trauma, and infectious trauma with the versatility of the reactions of the synovial cell produces a host of histologic alterations that may be difficult to identify and even more difficult to classify. It is not surprising, therefore, that neoplasms arising from the synovial tissue have defied satisfactory classification. Some of these enigmas have, however, been solved as a result of the brilliant tissue culture analyses of the synovial cell by Vaubel and by Murray and Stout. These studies have clarified the nosology of the malignant synovial tumors and have consolidated the heterogeneous entities previously described into one group—synovial sarcoma (or malignant synovioma). Classification of the benign tumors of synovia, however, is still in an unsettled state. Thus, the giant-cell tumors of tendon sheath (xanthomas) are considered by some to be truly neoplastic, by others to be an inflammatory reaction, and by still others to represent a manifestation of a lipoid disturbance. In all probability the final solution will be a subdivision of these benign tumors of synovia into neoplastic giant-cell tumors and metabolic giant-cell tumors (xanthomas).

From the point of view of treatment we require a classification of benign synovial tumors that will give us an un-

derstanding of the diagnostic approach the treatment tenets to be followed, and the expected end results Such a classification is one suggested by Morton. It is realized that this classification has certain shortcomings and may include in similar categories (giant-cell tumors) certain inflammatory lesions or manifestations of lipoid disturbances However it is much more dangerous to err on the side of calling a neoplasm an inflammatory lesion than to make the opposite mistake and regard some inflammatory or metabolic disturbances as neoplastic. A careful and critical review of the literature indicates that no harm can result from treating these tumors with proper surgical extirpation whereas the opposite policy of treating them as if they were all inflammations or metabolic disturbances could be disastrous.

Certain tumors have a predilection to form within certain parts of the synovial tissue. Thus synovial sarcomas arise most frequently from tendon sheaths or bursa and very seldom from intraarticular synovial tissue.

Ganglions most frequently arise from the tendon sheaths of the extensor tendons of the hands and digits Giant-cell tumors may be both intraarticular or extraarticular when arising from the joints, or they may arise from tendon sheaths or bursa.

Although these individual inclinations exist it is emphasized that each tumor whether arising from joint, tendon, sheath, or bursa, has the same parent tissue *and presents a similar natural history* Similarly although different tumors seem to prefer different sites, each may arise anywhere within the synovial system

CLASSIFICATION*

Benign Tumors

These tumors of synovial tissue include (1) ganglion, (2) giant-cell tumor (xanthoma) (3) benign synovioma, (4) fibroma, (5) chondroma or osteochondroma, (6) angioma (hemangioma and lymphangioma) and (7) lipoma.

Malignant Tumors

These tumors are all classified as synovial sarcomas. Common usage has applied the term *synovioma* to the malignant tumor of synovia. To change the name now and to use the term for a benign neoplasm could be confusing. Because of its established character we shall adhere to it in this treatise but emphasize that the qualifying adjective *malignant* should be added.

Metastases to Synovia

Metastases to any part of the synovial system are very rare and are usually part of a disseminated carcinomatosis

* Modified from J J Morton.

BENIGN TUMORS

GANGLION

Ganglions are true tumors of the tendon sheaths, although they have long been considered cysts or the results of degeneration of the tendon sheath. They are composed predominately of the lining membrane, whose cells are

[illegible]

INCIDENCE

[illegible]

CLINICAL COURSE

[illegible]

TREATMENT

[illegible]

cyst to another It is advisable to make the exposure under a tourniquet to provide a bloodless field. Careful dissection and visualization of the entire lesion will permit total extirpation and prevent recurrence. Too conservative an excision of these tumors without adequate visualization will result in a recurrence in almost 50 per cent of the cases

GIANT CELL TUMOR OF TENDON SHEATH (XANTHOMA)

Giant cell tumors of tendon sheaths are the second most common benign tumor of synovia, comprising, with ganglions, the majority of subcutaneous tumors of the hands and feet. The incidence of these neoplasms has not been truly discerned. Wright in 1951 reported 85 cases from Leeds England. A very detailed study was made by Calloway Broders and Ghormley of the Mayo Clinic where 70 patients bearing giant cell tumors were treated up to 1940 Many giant-cell tumors have been observed and treated by the authors

AGE AND SEX DISTRIBUTION

The tumors occur most frequently in middle-aged females The average age of Wright's series was 38.5 years with 67 per cent women The average age of those reported from the Mayo Clinic was 44 years Of 223 cases culled from the literature by Galloway *et al.* 71 per cent were women the average age was 37 5 years

LOCATION AND GROWTH CHARACTERISTICS

The tumors occur most often in the digits, on both flexor and extensor aspects of the tendon sheaths They usually grow slowly with an average delay of three years from the time they are first noted until treatment is sought. Initial rapid growth may be noted. A number of such instances have been reported by Wright and by Galloway Broders and Ghormley

ETIOLOGY

The etiology is unknown. In fact, their exact classification awaits elucidation. There are three main theories regarding their origin. The theory that these tumors are products of disturbances of lipid metabolism is favored by De Santo and Wilson and also by Galloway, Broders, and Ghormley who present as evidence the *so-called foam-cells* which are truly histiocytic and responsible for the deposition of certain lipid elements such as cholesterol A high cholesterol content of giant-cell tumors of tendon sheath has been recorded. In addition, a quantity of hemosiderin is noted within these tumors, due to the phagocytic activity of certain cells On occasion other evidences of generalized lipid disturbances are noted, such as a related xanthelasma or other subcutaneous xanthomas It may be stated in passing that there has been no significant coincidental occurrence of giant-cell tumors of tendon sheaths and such disseminated lipidosis as Niemann Pick disease, Hand Christian-Schüller syndrome, or Gaucher's disease.

In past years the tumor has been incorrectly called giant-cell *sarcoma* and many unfortunate patients have suffered needless amputation of a finger Malignant transformation of this tumor is of extreme rarity Geschickter and Copeland have postulated the theory that these tumors arise in rudimentary sesamoid bones they affirm their histologic similarity to giant-cell tumors of bone and call attention to the fact that these tumors usually arise at the sites of sesa



FIG 310 Xanthomatous giant-cell tumors of tendon sheath in an adult

moid bones These lobulated tumor masses may erode the underlying bone by pressure necrosis, but this does not indicate a malignant quality of the tumor Similar tumors containing xanthomatous deposits may develop as arborescent masses within larger joints, *e g*, the knee and ankle, these lesions have a greater tendency to become malignant than the common phalangeal giant-cell xanthoma

The group from Mayo Clinic made extensive studies of the lipids of the blood as well as of tumor lipids They found an increase in the total lipid content of the blood in patients with giant-cell tumors of tendon sheath They criticize the common practice of looking for a hypercholesteremia as the exclusive finding of lipemia They caution that there may not be an absolute increase in the blood cholesterol but there will be, almost universally, an increase in total blood lipid They believe that the tumor represents a localized manifestation of a disturbance in lipid metabolism The fact that many patients cite trauma as accelerating the growth of a stationary or slowly growing tumor is interpreted by Galloway and his associates to represent the addition of an exciting cause to a systemic disturbance which results in the formation of a tumor About 40 to 50 per cent of patients give a history of trauma

Others claim that these tumors represent an inflammatory reaction, a localized manifestation of a nodular villous arthritis These authors present examples of the fact that the adjacent synovia will frequently also show inflammatory reactions of overgrowth and papillary projection with villus formation The extent of the villus formation depends upon the stage of the disturbance, which in turn is the result of the duration of the disease at that particular site They suggest that the overt tumefaction represents a rather advanced stage of a diffuse process

Those who claim a neoplastic origin for these tumors merely have to cite the numerous exceptions to the above two theories, in which neither disturbance of lipid metabolism nor inflammatory reaction of the adjacent synovia is observed In addition Wright has been able to trace these tumefactions from highly differentiated and innocuous neoplasms containing many histiocytic elements through an intermediary stage to one where they are extremely cellular and infiltrate

A review of the accompanying illustrations reveals the diffuse nature of certain giant-cell tumors of tendon sheaths,

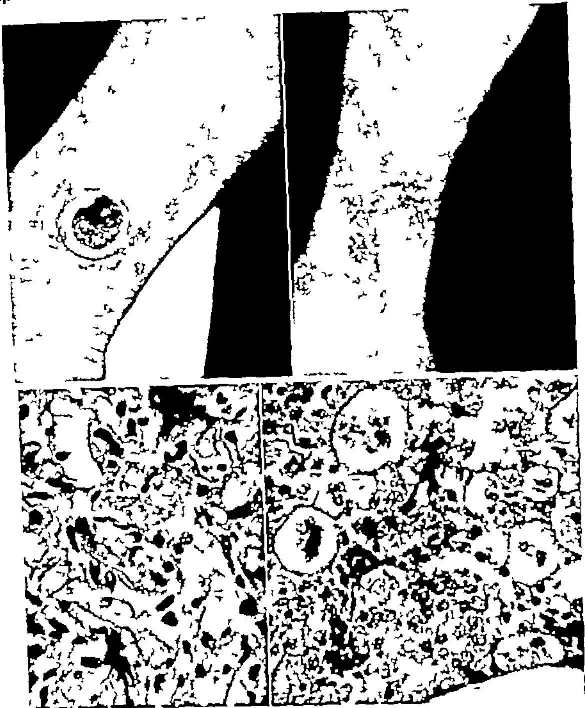


Fig. 311. (*Upper left*) Benign ulcerating xanthoma of skin of ankle, treated by surgical excision and skin-grafting (*Upper right*) End result 5 years later (*Below*) High-power photomicrographs of xanthomatous tumor of tendon sheath.

especially the multiple ones associated with similar lesions in the skin and other structures and suggests that they should be considered a form of lipoidosis The solitary giant-cell tumors of tendon sheaths are considered by Stout as a subgroup of the xanthomas and he calls attention to the fact that on occasion giant-cell tumors of bone may be an accompaniment of giant-cell tumor of tendon sheath.

GROSS CHARACTERISTICS

These tumors tend to grow as nodular overgrowths and their size is frequently determined by their location. They are usually painless Those of the fingers tend to remain small and nodular and vary in size from 1 to 2 cm. in diameter whereas those occurring more proximally may grow as large as from 6 to 7 cm in diameter This is probably the result of



FIG 312 Photomicrograph showing cholesterol crystals in giant-cell xanthomatous tumor of tendon sheath



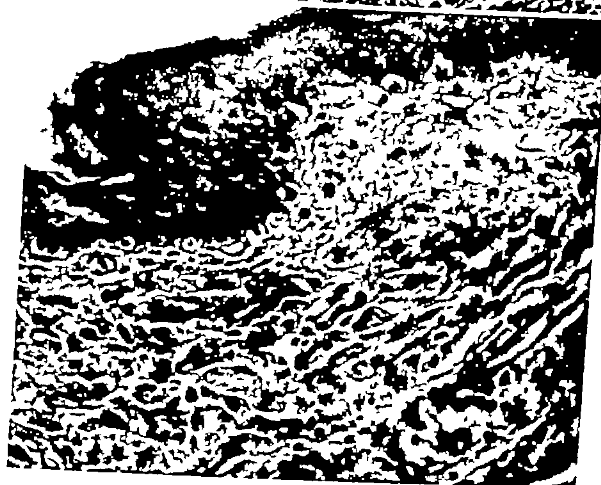


FIG 313 Xanthelasma Photomicrographs showing lattice fibers (*gitterfasern*) lying between and surrounding the foam cells

the inhibiting factors within the tumor bed The structure of the fingers does not yield easily, and as the tumor grows in an expansile manner, it ruptures the tendon sheath and then extends subcutaneously An occasional instance has been reported in which the tumor has been attached to the overlying skin Those tumors which arise in the flexor aspects of the digits generally develop a groove through which the flexor tendons rise Those occurring in the popliteal space, a roomier tumor bed, can grow in a fungating polypoid manner

Giant-cell tumors are usually grey in color but may vary from a dull grey to a golden yellow and thence to a greenish red There may be an intermingling of the various tinctorial elements The color differences are a result of the different cellular elements, fat (which gives the yellow hue) or blood pigment (which gives the reddish-brown-green hue)

HISTOLOGY

The histology of the giant-cell tumors reflects the diverse structure of synovial membrane and includes foam cells, the fibrocellular stroma, blood vessels, blood pigment, and multinucleated giant cells A rather interesting feature is the absence of any secretory substance, which is in contrast to the ganglion and its secretory ability It appears that the giant-cell tumors are less differentiated and therefore have lost their secretory ability Hyaluronic acid is not usually found within them, although an occasional report of synovial tumors describes a high hyaluronic acid content

The relative amount of phagocytes containing lipid varies with different tumors and even in different locations of the same tumor When abundant, the tumor resembles a granuloma In other

tumors a dense fibrous structure similar to that of a fibroma dominates the topog raphy Different giant-cell tumors show all gradations

RECURRENCE RATE

Recurrences following the treatment of giant-cell tumors of synovia are rather high. Although Willis Ewing, and Characho report them to be uncommon, Regars and Shively reported 3 recur rences in 23 cases Galloway *et al* recorded 9 recurrences in 61 cases and Foster recorded 3 recurrences in his 42 cases Wright records a 44 per cent recurrence rate in 56 patients

TREATMENT

All benign giant-cell tumors should be treated surgically Local excision usually suffices Excision following recurrence should be more drastic and more radi cal. Because they tend to arise from a broad base or to be composed of several fused nodules careful and meticulous dissection with adequate exposure is mandatory



FIG. 314. Examples of cutaneous xanthomas in three different patients.

XANTHOMATOSIS

The following discussion is presented because of the frequent association of xanthomatosis and giant-cell tumors of tendon sheath

CLASSIFICATION

Xanthoma tuberosum is a condition in which multiple tumors of yellow to orange color often symmetrical in distribution, occur subcutaneously on the extensor surfaces especially of the knees elbows, ankles, buttocks, trunk, hands and feet. They vary in size from 3 mm. to 5 cm. or more in diameter They occur in groups which coalesce to form larger orange-colored agminated masses The lesions are commonly attached to tendon sheaths

This entity may be roughly divided into two categories first, a non inherited, infrequent, sporadic form, occurring in adults with or without disturbances of fat metabolism, not fol lowing the usual natural history of the disease, and never involving the mucous membranes and second, the classic familial type, frequently developing dur ing childhood and usually associated with hypercholesteremia and sometimes with other important metabolic disturbances Gossage has maintained that the inheritance of xanthomatosis is through a single dominant factor

The etiology is still doubtful, the fre quent coexistence of hypercholesteremia and other dysfunctions of lipid metabolism is significant, but as far as we

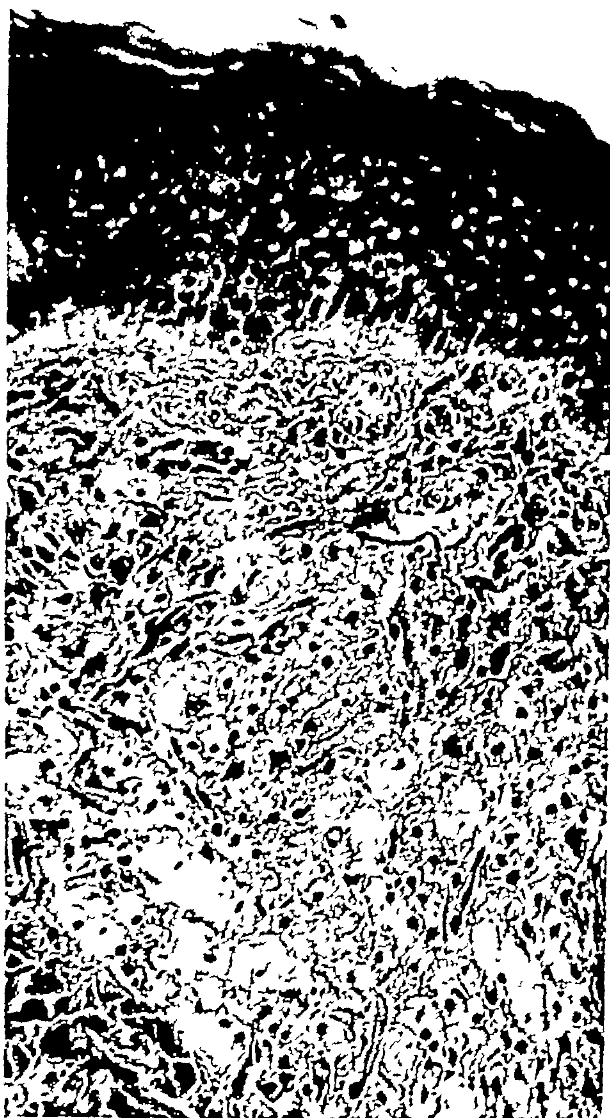


FIG 315 Xanthoma tuberosum multiplex Photomicrograph showing characteristic foam cells

know, xanthomas have never been produced by the injection of cholesterol or by artificial hypercholesteremia The nodular tumors could represent reactive phenomena of the tissues at the site of deposits of cholesterol and other irritating lipids Hamilton, Montgomery, and Osterberg studied the blood lipids in ten patients with xanthoma tuberosum and found an increase in total cholesterol and total lipids They discovered the cholesterol to be elevated at the expense of the fatty acids When the hyperlipemia was marked, however, the total cholesterol did not show as great an increase and therefore was in lower proportion to the total lipids

Xanthoma diabeticorum is an acquired xanthomatosis, in which the nodules develop in diabetic patients with severe hyperlipemia but regress when the diabetes is properly treated by diet and insulin.

Xanthomatosis disseminata refers to a diffuse yellowish-red coloration of the skin, associated with fine papular lesions It may be distributed on the flexural as well as on the extensor surfaces of the skin and may have no associated disturbances of blood lipids A pathognomonic feature of xanthomatosis (especially in xanthoma tuberosum multiplex) is the bizarre picture produced by the orange-colored xanthomatous infiltration that follows exactly the lines of the palm

Xanthomatosis with multiple deposits in bone, producing the radiographic appearances of vertebra plana, were independently described by Jansson in 1935 and Davies in 1949

Xanthoma palpebrarum or *xanthelasma* is the flat yellow plaque occurring bilaterally in the loose tissues of the eyelids Xanthelasma may or may not be associated with xanthoma tuberosum, but the accompaniment is frequent enough to attribute a relationship to systemic disturbances in lipid metabolism. On microscopic study very few Touton giant cells are seen, and there seems to be a definite increase in the lattice fibers (*gitterfasern*) lying between and surrounding the foam cells (see Fig 313)

Juvenile xanthoma is identical with familial xanthoma tuberosum in its pattern of inheritance, hyperlipemia, distribution, and character of tumors. In the juvenile cases serious degenerative changes are coexistent in the heart, arteries, and liver It is true that sudden heart failure does occur in adult patients who have xanthoma tuberosum and that children may die as the result of arteriosclerosis without evidence of xanthomatosis, nevertheless, the frequent association of the hereditary predilections for xanthomas and of heart disease in infancy and childhood, the coexistence of

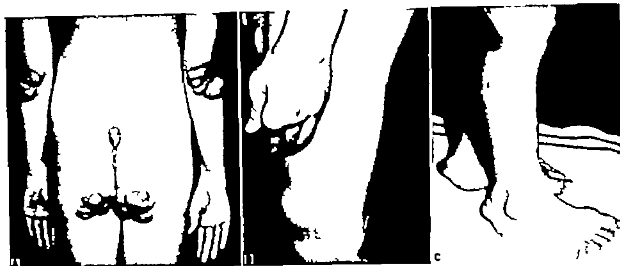


Fig. 316 Diffuse xanthomatosis in a young child which had been present since infancy and had been gradually progressive. A. Lesions involving the buttocks and elbow B Xanthomatosis involving the dorsum of the left hand. C Lesions involving the feet and leg

xanthomas and arteriosclerosis in juveniles and the reports of sudden death during adolescence of patients with xanthomas offers convincing proof of this relationship Postmortem examinations of these young people have demonstrated severe cardiac disease involving the mitral valve, myocardium, and coronary arteries According to Rigdon and Willieford, the cause of sudden death in this group is commonly occlusion of the anterior descending branch of the left coronary artery Rigdon and Willieford have offered the following explanation of the manner of formation of the sclerotic plaques "The lipoid cells appear in the intima in the largest number at the junction of the intima with the media, and these cells increase to form the intimal plaques degeneration and fibrous proliferation occur within the plaques, and the media beneath the plaques degenerates as shown in the variation in staining of the elastic fibers Calcium may or may not be present in these cases"

HISTOPATHOLOGY

The lesions develop in the corium and subcutaneous tissues and also in the tendon sheaths and synovia. The histologic picture is typical and diagnostic, featured by the large vesicular foam cells with netlike protoplasm. The Touton type of giant cell with numerous peripheral nuclei forming an uninterrupted circle is found in the tuberous type of xanthoma The xanthoma or foam cells are in intimate relationship with capillaries and smaller blood vessels in the superficial cutis The number of lattice fibers (*gitterfasern*) is increased. There is much interstitial fibrosis, which proliferation may be secondary to the irritation by the cholesterol deposits that are sometimes visible. It is still a moot question whether the xanthoma is a true neoplasm or a granuloma.

TREATMENT

Treatment of the large, disfiguring, or disabling xanthomas is surgical excision although this seems futile because of the



Fig. 317 Coexistence of xanthelasma xanthomas of tendon sheaths, and interdigital subcutaneous xanthomas.

widespread and systemic nature of the disease Urbach has advocated a low-fat, low-cholesterol diet for these patients, several reports have appeared of regression and even disappearance of these tumors through a dietary regimen

LIPOMAS OF SYNOVIAL TISSUE

The universal distribution of fat makes it possible for lipomas to arise even in the tendon sheaths and joints

There are two main types of lipomatous tumors arising from synovial tissue 1 *Simple lipomas* tend to occur as congenital anomalies, presenting as bilateral tumefactions on identical sites, usually on the extensor tendon sheaths of the digits Their soft consistency (sometimes firmer when arising from the digits), radiolucency, asymptomatic nature, and slow growth should be pathognomonic of lipomas but they are very rarely diagnosed before operation 2 *Arborescent lipomas* Charache has likened the fat of the joints or tendon sheaths to that of the appendices epiploicae Both fatty deposits may give rise to a diffuse, arborescent type of fatty tumor. In addition to the usual fat cells, these tumors contain an abundant fibrous tissue and vascular elements They have been termed *fibrolipomas, hemangiolipomas,* etc Because these tumors usually arise from a broad base, good exposure is mandatory for their complete exploration Occasionally these tumors may contain nerve elements and may be painful and tender As a rule, however, the lipomas are asymptomatic and occur in middle-aged males as a slowly growing mass. With growth, dysfunction, paresthesia and pain may develop as a result of pressure upon neighboring structures

Their rarity is evidenced by the detailed study of Straus, who collected only 25 cases up to 1935. Since then a similar number have been reported

Grandclaude, Razemon, and Bizard record an angiolipoma of the pollicis longus flexor tendon which produced a spontaneous rupture of the tendon Gosselin and Straus have noted an increase in the consistence of lipomas when chilled and have advised the procedure as a preoperative diagnostic test

TREATMENT

The treatment is surgical excision, care being taken to obtain good exposure, especially for the arborescent type A pedicle can usually be identified, and its severance will permit complete removal of the tumor. Recurrences are rare No instance of malignant degeneration has been reported

BENIGN SYNOVIOMA

The term *synovioma* should be reserved for the malignant synovial tumor However, an occasional benign tumor of synovia, which does not have the histologic structure of giant-cell tumors but reproduces synovial tissue has been designated benign synovioma by Stout, from whom the following paragraph is quoted

Very occasionally one or more tumor-like nodules have been found in the capsule of the knee joint These are made up of a stroma of adult fibrous tissue and many devious, sinuously twisted slits lined by prominent but otherwise normal synovial cells Whether or not these are simply localized hyperplasias of synovial tissue or true neoplasms is unknown All that can be said is that they reproduce exactly, but in adult differentiated form, the structural composition of the synovial sarcoma and are benign

MISCELLANEOUS BENIGN TUMORS OF SYNOVIAL TISSUE

The supporting structure of synovial tissue permits development of such tumors as hemangiomas and lymphangiomas. The reported fibromas of tendon sheaths (of which there are about 100) possibly represent a phase of giant-cell tumors in which the fibrous element dominates The close anatomic association of synovial tissue to cartilage and bone favors the development of chondromatous or osteochondromatous tumors Certain of these latter may represent metabolic or inflammatory lesions especially the multiple chondromatosis of the joint capsule.

The treatment of each of these conditions is surgical resection, and the prognosis is uniformly good.

CASE REPORT NO 59: MULTIPLE CHONDROMAS OF TENDON SHEATH

J Q a 33-year-old male was first seen on September 16 1937 In 1932 he observed a small spherical nodule situated subcutaneously on the proximal phalanx of the right middle finger Eighteen months later a second nodule developed on the lateral aspect of the same finger When seen in 1937 eight subcutaneous nodules were palpated along the right middle finger and extended into the palmar aspect of the hand. These nodules varied in size from 3 mm to 1½ cm in diameter

On September 17 1937 a surgical dissection was performed. The nodules on exposure were found to be firm glistening, grayish white in color and to be attached to the tendon sheath of the flexor digitorum sublimis tendon. Two of the nodules were free within the tendon sheath. The exposure was made in a vertical direction, beginning at the distal flexion crease of the palm of the hand and extending down almost to the interdigital flexion crease of the middle finger The tendon of the flexor digitorum sublimis was exposed, and the nodules were dissected free Under the

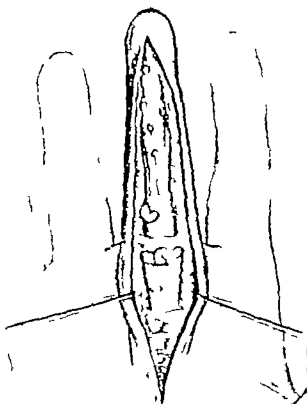


Fig. 318. Congenital multiple chrondromas of tendon sheath.

microscope they were found to be multiple benign chondromas It was thought that they represented miniature sesamoid bones. One additional nodule was removed several years later but the patient is now in excellent health and has good use of his hand and no evidence of recurrence

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MALIGNANT TUMORS

SYNOVIAL SARCOMA (MALIGNANT SYNOVIOMA)

Sarcomas arising from synovial tissue constitute an interesting clinicopathologic entity Although the histologic features and nosology have been adequately described, certain clinical aspects, including the natural course,

proper methods of treatment, expected end results, and factors which influence prognosis, have not been well established

This review analyzes the pathologic and clinical features of 60 patients with synovial sarcoma

DEFINITION AND NOMENCLATURE

Synovial sarcoma in this presentation represents those malignant neoplasms which arise from synovial tissue of joints, tendon sheaths, and bursae and present histologic features characteristic of synovial tissue

The term *synovioma,* introduced by Lawrence Weld Smith in 1927, has been popularly accepted to designate malignant tumors of synovial tissues Smith followed the time-honored embryologic custom of designating a tumor by the type cell from which it derives This is perhaps unfortunate, because the term etymologically connotes benignity However, because of its universal usage and because of the tragic consequences which might result from lack of complete understanding of definition between pathologist and surgeon, the term will probably continue in use If used, it is desirable to attach the prefix *malignant* to synovioma to emphasize the nature of the tumor. Since the term *synovioma* has been used generally for malignant neoplasms, it should never be employed to designate a benign lesion

Certain complex ambiguous names adopted to label malignant synovial neoplasms and based on misconceptions concerning the true nature of synovial tissue should be discarded Some of these terms include sarcoma fusoglobocellulare, villous angiofibroperithelioma, synovial sarcoendothelioma, adenosarcoma, reticulohistiocytosarcoma, epitheliosarcoma, sarcomatous perithelioma, mesothelioma, fibroendothelioma, synovial endothelioma, etc The word *endothelioma* should be avoided because its connotation is so obscure when not limited to vascular tumors

HISTORIC REVIEW

According to Berger, the first recorded instance of synovial sarcoma was apparently by Stur in 1893 A tumor of the tendon sheath was described by Chassaignac as early as 1852 (Gaz Hop, 1852, p 185 Cancer de la Gaine des Tendons) The first adequately described and proved case is that reported by Lejars and Rubens-Duval in 1910 Thereafter, a number of individual case reports describing the cytologic features of malignant synoviomas comprised the essential contributions until Lawrence Weld Smith in 1927 presented a pathologic and clinical description and introduced the term *synovioma* Additional case reports by Wegelin (1928), Prym (1930), Wagner (2 cases, 1930), and Diaz (1931), who reviewed the literature to that date, aided in establishing this malignant tumor of synovial tissue as a distinct entity Sabrazes and associates (1932) focused attention upon the malignant neoplasms of joints and contributed to an understanding of the pathogenesis of malignant synoviomas Leila Charlton Knox in 1936 reported three cases observed at St Luke's Hospital, New York, and gave a detailed description of the clinical and pathologic features A thorough study of the pathologic characteristics of five cases was made by Berger in 1938, and his critical review of the reported cases in the literature presented the cumulative knowledge of this malady to that date He collected but twenty-one authenticated cases of synovial sarcoma (including five of his own cases) from the world literature to 1938

Berger further analyzed carefully the reported cases of tumors arising from the bursae, articular surfaces, and tendon sheaths and established the fact that neoplasms arising from each of these

sites originate from the same type of tissue (synovial tissue) and hence should be classified under the same oncologic heading, *synovial sarcoma* There is a greater frequency of tumors of the tendon sheaths less common are those of the joint capsules, and of still greater rarity are those that involve the serous bursae.

The nosology of synovial sarcomas must of necessity depend upon the nature of synovial tissue, and various theories have been advanced to define synovium. Some of these are given below

1. It is an epithelial structure (von Kolliker Soubbotine, and Mayeda) which possesses the ability to secrete an articular fluid.

2. It is an endothelial tissue (Bichat, His, Kaufmann, and Aschoff)

3. It represents modified cartilage (Lubarch) or is derived from cartilage (Tourneux)

4 It is a very cellular connective tissue (Heuter Hagen Torn, and Hammar)

5 Synovial cells belong to the reticuloendothelial system and as such are active in the transformation of blood pigment and in phagocytosis (Franceschini and Sabrazes et al.)

6 Synovium represents a specialized, differentiated type of mesodermal cell. It produces as its ground substance a mucinous material and consequently may be classified in the same category as cartilage and bone, which cells elaborate a ground substance. The essential differentiation between the ground substance of cartilage and of bone and synovial tissue is that the former two are solid, while the last is liquid, particularly adapting it to its function of lubrication of the joint surfaces (Vaubel)

The synovial cell has an inherent propensity to line surfaces and functionally may adapt itself to such a purpose, as for example, following synovectomy when a new synovial lining may regenerate within a joint.

As a result of these divergent views, neoplasms arising from synovial tissue have followed the same theories and have thus been ascribed to different tissue types Thus, malignant *synoviomas* have been considered by some to be derived from endothelial structures and hence were called *endotheliomas* (Lejars and Rubens-Duval, and Wagner) Others attribute a histiocytic nature to synovial tumors (Berger and De Santo *et al.*) while more recent authors ascribe to the belief that the prototype cell from which synovial tumors originate is a specialized type of mesothelial cell (Knox, Morton, Haagensen, and Murray Stout and Pogogeff)

Murray Stout and Pogogeff cultivated cells in vitro from three human synovial sarcomas and noted that their characteristics compared with normal synovial tissue. They considered the normal synovial cell to be a specific cell type distinct from epithelium and from the fibroblast. They have classified the synovial sarcoma as a distinct neoplasm exhibiting similarities to the mesothelioma. An excellent presentation of sixteen cases by De Santo Tennant, and Rosahn in 1941 correlated the pathologic characteristics with the clinical courses and evaluated the therapeutic attempts to eradicate the neoplasm. Reports of four cases by Jaffee and Lichtenstein (1941) and five cases by Briggs from the Army Medical Museum (1942) aided further in establishing the clinicopathologic features of synovial sarcomas

Haagensen and Stout (1944) after establishing criteria for diagnosing synovial sarcoma derived from tissue culture studies of both normal synovial tissue and synovial sarcoma, studied all reported cases in the literature (which numbered 95) and added 9 cases from their own experience. These authors emphasize the over all poor results obtained in the treatment of synovial sarcoma.

INCIDENCE

During a twenty-year period, 60 patients with *synovial sarcoma* were treated. This group represents all patients seen with the neoplasm, regardless of the stage of the disease and whether definitive therapy was given or not A microscopic diagnosis was established in every instance Synovial sarcoma comprises 8 3 per cent of all malignant neoplasms of the soft somatic tissues in the authors' series.

AGE AND SEX

There is no preponderance for either sex in this series Thirty patients were males, and thirty were females Others have described a predilection for the male sex

Synovial sarcoma is essentially a disease of younger adults Sixty per cent of the tumors in this series occurred in patients between the ages of 15 and 40 years The average age of the group was 36 3 years The youngest patient was 2 weeks old when the tumor was first noted, and the oldest was 68 years The average age for the males was 36 7 years, not significantly different from 35 9 years, the average age of the females in this same series.

ETIOLOGIC FACTORS

There were no specific etiologic factors for the production of synovial sarcoma established in this series. In certain instances a contributory relationship appeared to exist between the development of the cancer and such factors as trauma, the malignant degeneration of a benign tumor, and others

A *The role of trauma* Trauma, usually a single injury, was related by nine patients as preceding the development of a mass The trauma was usually of a severe nature In five of the cases, the mass appeared immediately or shortly after the trauma, which suggests strongly that trauma merely called attention to the tumor or possibly that hemorrhage occurred within the tumor, increasing its size In one instance a tender mass developed two months following injury One patient suffered trauma to the thigh on repeated occasions for a period of three years, after which a tumor developed at the same site, remained stationary for six years, and eventually was excised. In one instance a traumatic amputation of an index finger was followed in eighteen months by a malignant synovioma in the stump No conclusions from these observations are warranted concerning the role of trauma in inciting tumor growths. One patient, a 52-year-old baker, constantly traumatized his elbow while taking bread out of the oven. He developed a synovial sarcoma at the site of these numerous exiguous traumas (See Fig 12)

B *The question of benign tumors of synovia undergoing malignant changes* is raised in three patients of this series in whom masses stationary in size had been present for 7, 30, and 10 years, respectively, after which rapid growth occurred Each of these developed in the hand, and two of the three were exceedingly malignant

C *A congenital relationship* is suggested in case report No 60 in which the neoplasm was noted when the child was 2 weeks of age

D *Infections, etc* One patient presented a history of rheumatic fever with pain and swelling of both knees and ankles for many years. She developed a malignant synovioma of the left knee No instance in this series suggested chronic bursitis or synovitis as a precursor in the development of synovial sarcoma. No etiologic relationship was observed between the occurrence of sarcoma of synovia and occupation, race, or nationality of the patients No metabolic abnormalities were observed, and

blood chemical studies, when performed, were normal in all instances

LOCATION

Synovial sarcomas occur most frequently in the extremities The lower extremity was involved in 34 instances 56 6 per cent) the upper extremity was the site of a malignant synovioma in 24 cases (40 per cent) and 2 synoviomas (3 4 per cent) occurred in bursae of the abdominal wall. The right side was involved in 39 instances while the left side of the body developed synoviomas in 21 cases of this series

TABLE 59 LOCATION OF 60 SYNOVIAL SARCOMAS

Anatomic Site	Number of Patients	Percentage of Total
Lower extremity	34	56 7
Thigh (including groin and buttock)	8	13 3
Knee	13	21 7
Ankle	0	0 0
Foot	11	18 3
Toe	2	3 3
Upper extremity	24	40 0
Shoulder	4	6 7
Elbow	2	3 3
Wrist	6	10 0
Hand	10	16 7
Finger	2	3 3
Abdominal wall	2	3 3

The knee was the most frequent location for the origin of malignant synovioma (21.6 per cent) The foot was next in frequency (18.4 per cent) The hand was third in order being the site for synovial sarcoma in 16 6 per cent of all cases The observation that the hands and feet are such frequent locations for malignant synoviomas warrants emphasis. At this institution synoviomas are the most frequent sarcomas observed in the hands and feet. (Table 59)

Another interesting feature concerning

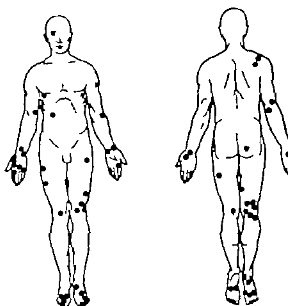


FIG 319. Scattergram illustrating the glonal distribution of malignant synovion Observe the predilection for knees, hands, a feet. (Pack and Ariel, Surgery 28 1047 195



FIG. 320 Clinical illustration of a syno sarcoma arising from the plantar aspect of left foot. An amputation of the fifth toe metatarsal bone was followed in one month a local recurrence and metastases to the d iliac lymph nodes for which a disarticulat of the left hip joint was performed. Generall metastases, however became manifest and patient died 4 months after the original op tive procedure.

the location of synovial sarcoma is observation that articular surfaces are infrequently involved by malignant s oviomas Most of the lesions arise in sues adjacent to articular surfaces in extraarticular sites, originating fr tendon sheaths and bursae. In his ea report L. W Smith commented on th four sites of origin, namely (1) sy vial membrane of the joint cavity (synovial membrane of overlying burs (3) tendon sheaths, and (4) fas



FIG 321 Synovial sarcoma of the palmar surface of the right hand The tumor incorporates the tendons of the palm (Pack and Ariel, Surgery 28 1047, 1950)

aponeurosis in the neighborhood of the joint

Granville A Bennett has stated "Bursal spaces lined by synovial membranes may develop in connective tissues of the body because of certain mechanical influences such as the massage of soft tissue over an acquired abnormal bony prominence or irritation caused by imperfect repair of an injury to bone such as pseudoarthrosis—the possible development of synovial tissues from other mesenchymal tissues when appropriately stimulated explains the occurrence of synovial membrane tumors in regions which are well removed from the articulations themselves" For example, synovial sarcomas occurring in the upper arm or thigh may not show any gross connections to structures having a recognizable lining of synovial membrane, and hence the histogenesis of the neoplasm is not suspected until a microscopic study has been done



FIG 322 Synovial sarcoma involving the index finger in a 45-year-old male Note the similarity of this neoplasm to benign giant-cell tumor of tendon sheath This malignant tumor recurred after local excision, and the recurrence was treated by deep x-ray therapy and amputation of the digit The patient remains well 15 years after treatment

GROSS PATHOLOGY

Grossly, the tumor may be either encapsulated, circumscribed with a pseudocapsule formed by pressure from contiguous structures, or it may be diffuse, infiltrating surrounding structures, producing distortion of bones from pressure, or infiltrating adjacent bones (Fig 323). The pseudoencapsulation may appear to be so real that the surgeon may wrongly decide that simple enucleation insures complete removal in a particular case In the course of local re-



Fig. 323. Gross specimen of synovial sarcoma of left foot. Note infiltration of os calcaneus. Pulmonary metastasis occurred 5 years after amputation. (Pack and Ariel, Surgery 28 1047 1950)





Fig. 324. Synovial sarcoma of right index finger (*Top*) Hand following amputation of index finger and metacarpal bone. Patient is well 10 years after amputation. (*Bottom*) Gross specimen showing the resected synovial sarcoma.



FIG 325 Synovial sarcoma of the palmar surface of the right hand Dissection showing the interlobulations of the neoplasm and smaller cystic areas dispersed throughout Note how the neoplasm incorporates all tendons of the palm

moval of a synovioma, the neoplasm is usually found to be securely attached to tendon sheath or joint capsule which represents either the site of origin or invasion. Occasionally pseudopodialike extensions may emerge from the main tumor mass

The size varies with the stage of the disease Although synovial sarcomas may assume huge proportions, they are usually not large, varying from 4 to 8 cm in diameter.

When the neoplasm arises from tendon sheaths, especially in the hand or foot, it may extend to incorporate adjacent tendons and other contiguous structures within the growth, and frequently it is not possible to determine the exact site of origin (Fig 325) When they originate in a digit, the growth may extend toward the surface, and the neoplasm presents itself as a subcutaneous nodule, or it may circumscribe the digit until the entire structure is involved by the cancer Synovial neoplasms of the hands or feet are either intimately adherent to contiguous bones or invade bone, so that it is impossible usually to separate the neoplasm from the tumor bed (Fig 326) Synovial sarcomas that arise from bursae frequently present a circumscribed mass which may present externally or infiltrate diffusely into surrounding muscles The tumor may be molded by the configuration or density of the tissues or direction of the tissue planes in which it grows

Those which arise within the articular surfaces appear as fleshy, greyish-red, succulent masses Cut-section usually reveals an interlacing maze of fiberlike strands, winding in all directions and presenting a glistening, ropy surface Sporadically situated in this firm, glistening maze of solid tumor are smaller and larger cystic cavities These cavities are frequently filled with a thick, tenacious, gelatinous fluid which may be of a clear amber color but not infrequently is discolored a dirty red, probably because of disintegrating blood Besides the cystic regions, small hemorrhagic areas are also noted Scattered throughout the section may be small foci of a butter-yellow color with other areas of calcification Occasionally small regions



FIG. 326 (*Left*) Clinical appearance of a synovial sarcoma of the second toe that completely surrounded the digit and later produced inguinal metastases. Generalized metastases eventually occurred, as a result of which the patient succumbed. (*Right*) Gross specimen (enlarged 2½ times) of the tumor shown in left figure, demonstrating the lobulated, cerebriform appearance of the cut section, cystic hemorrhagic foci, and intimate attachment to bone. (Pack and Ariel, Surgery 28 1047 1950)



FIG. 327 Gross appearance of two synovial sarcomas of thigh. (*Left*) Cut section of synovial sarcoma of thigh from which metastases spread to the iliac nodes and became generalized. The patient died one year after operation. (*Right*) Cut section of synovial sarcoma of the right upper thigh which produced metastases to the inguinal nodes 6 months after wide surgical excision. (Pack and Ariel, Surgery 28 1047 1050)

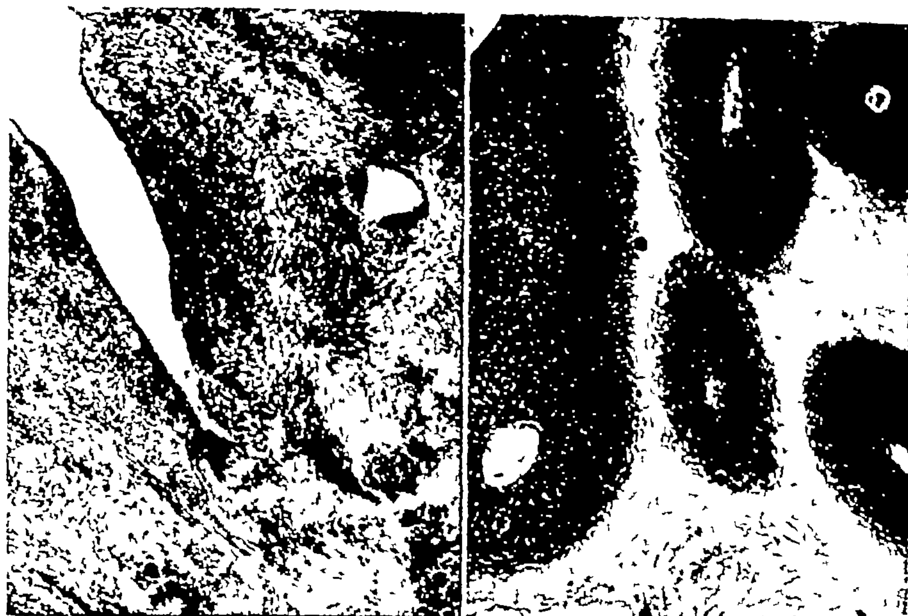


FIG 328 Photomicrographs of synovial sarcomas (*Left*) Demonstrating characteristic pathognomonic clefts lined by mesothelium and simulating synovial spaces The synovioma is largely fibrosarcomatous (*Right*) Perithelial type, persistence of tumor around vascular core

of cartilage or bone may be observed (Fig 327)

Different tumors vary in the relative amounts of diverse structures they present on cut-section Some may be almost entirely solid and fleshy while others have relatively small amounts of solid structure. The bulk of the mass is composed of hemorrhagic or cystic regions All degrees of variations are observed The firmness of the neoplasm varies, of course, with the structure, from the softer lesions which are cystic or cellular to the dense fibrosarcomatous types

MICROPATHOLOGY

When one recalls that normal synovial tissue consists of two layers (an outer fibrous-tissue layer and an inner layer of dendritic cells often forming villi), usually so intimately fused that grossly it is difficult to distinguish the separate layers, it is not surprising to observe the same cell types comprising malignant tumors of synovial origin The two component parts may be completely separate, or more frequently they are intimately mingled The synovial cells lining the articular spaces have their origin from the same mesenchymal tissues from which the fibrous and hyaline cartilaginous portions of the skeletal parts arise

The pathognomonic cell type is an epithelioid cuboidal cell, with a large vesicular nucleus and acidophilic cytoplasm which apparently attempts to reduplicate structures assumed by normal synovial cells They may form solid nests and adopt a fusiform shape. More frequently they attempt to form villi with papillary projections extending into a cyst lumen The shape of the cells that surround the cystic lumina varies from those which are flattened to others which may be cuboidal or high columnar The cystic lumina are usually filled with a mucinlike material It is this mucinous groundwork which gives a gelatinous appearance to the gross structure The cystic spaces may vary in size from microscopic slits to large cysts It is these structures, the cystic spaces surrounded by epithelioid cuboidal cells projecting in villous fashion into the space, that constitute one of the most characteristic features of synovial sarcoma (Fig 329) Small, red-staining intracellular droplets of mucin are noted

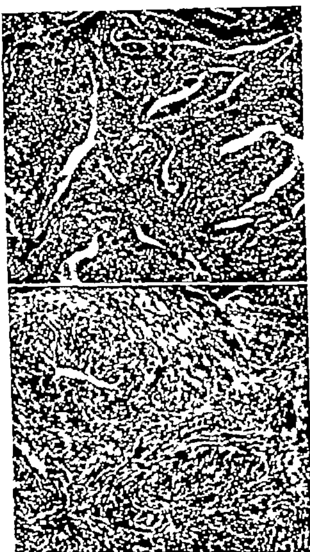


FIG. 329 (*Top*) Microscopic appearance of papillary type of synovial sarcoma, a common variety

FIG. 330 (*Bottom*) Microscopic appearance of spindle-cell type of synovial sarcoma another common variety (Pack and Ariel, Surgery 28 1047 1950)

when stained with mucicarmine, which is an important pathognomonic and diagnostic feature. The mucoid substance secreted by the tumor cells is said to contain hyaluronic acid, a constituent often found in joints

Fibrous-tissue elements are ever present throughout the tumor These may manifest themselves as dense sheets of malignant spindle cells producing the typical appearance of spindle-cell fibrosarcoma (Fig 330) In such instances a careful search through numerous sections may be necessary to identify the pseudoglandular clefts characteristic of synovial sarcoma. In other instances the

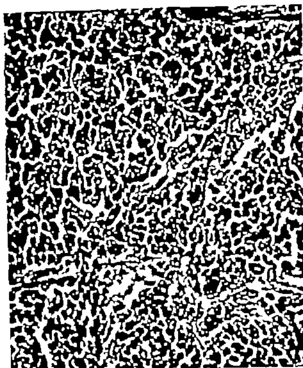


FIG 331 Photomicrograph demonstrating anaplastic nature of a synovial sarcoma.

synovial elements predominate, and the fibrous elements merely lend support to the attempts at glandular formation by the synovial elements They usually form the central core for the papillary projections

Every degree of differentiation may be noted in the fibrous-tissue cells varying from cells that are markedly anaplastic and form distorted spindle shapes with marked loss of polarity and hyperchromatism (Fig 331) to complete differentiation with apparently normal fibroblasts and fibrous tissue. All degrees between these extremes can be observed. Silver stains may serve to identify the fibrosarcomatous components by blackening the reticulin fibers Silver staining enables one to determine the proportions of fibrosarcomatous and synovial elements

Blood vessels are usually numerous throughout the specimens, some of which may be ruptured. Certain tumors are characterized by sheets of synovial like cells arranged about a central blood vessel producing a perithelial appearance. Occasionally calcification and *more rarely* chondrification or osteo-

genic formation may be noted Numerous lipophagic and siderophagic elements may be encountered frequently

The diagnosis can usually be established by the presence of the characteristic cell type, containing intracellular droplets which stain red with mucicarmine, and the presence of clefts lined by flattened or cuboidal cells Even in those instances in which the tumor is made up almost exclusively of spindle cells, the distinction from fibrosarcoma can be made usually by careful search for the aforementioned pathognomonic features, although the search may necessitate many sections Different tumors display varied degrees of malignancy as determined by the usual microscopic criteria The clinical course is determined usually by the degree of malignancy noted microscopically In general, the cellular synoviomas may be said to be somewhat radiosensitive and to have a tendency to metastasize to regional lymph nodes, whereas the synovial fibrosarcomas, in contradistinction, are relatively radio-resistant and seldom metastasize locally

Granville Bennett has enumerated some of the common histologic patterns formed by the malignant synoviomas (1) undifferentiated connective-tissue type, (2) formation of tissue spaces which vary from slitlike clefts to well-defined glandlike spaces containing serous or mucinous fluid, (3) formation of cell tufts, varying from compact groups of oval or polygonal cells segregated in solid portions of the tumor, to papillary projections extending into the clefts and glandlike spaces, and (4) the more characteristic tumor, consisting of reproduction of epitheliumlike cells upon a supporting stroma of compact tissue formed of elongated cells with small dark nuclei

METASTASES

Metastases from malignant synovioma are usually by means of the blood stream, and the most frequent location for metastatic deposits is the lung Pulmonary metastases were observed in 39 patients (65 per cent) The average time from treatment at the hospital until pulmonic metastases became evident was 15 9 months Any organ may be involved by diffuse metastases from this tumor, and widespread intraabdominal metastases were frequently observed after the disease had become generalized

A unique feature of synovial sarcoma is its tendency to metastasize to regional lymph nodes This characteristic must be considered in any therapeutic attack Involvement of regional lymph nodes (axillary and inguinal) was observed in ten instances of this series (16 6 per cent) Haagensen and Stout list eleven instances of regional lymph-node metastases

Another interesting feature concerning metastases from malignant synovioma is the fact that they may metastasize to bone Five such instances were observed in the present series (8 3 per cent). One was in the skull, one was in a thoracic vertebra and involved the spine, two were in the pelvis, and one in the femur

The duration of time for distant metastases to manifest themselves subsequent to therapy varies from three months to five years As a rule, however, these data demonstrate that at the outset the course of the disease is usually slow, and metastases develop late

SYMPTOMS

There is unfortunately no symptom complex which characterizes synovial sarcoma and which serves to differentiate this malignant neoplasm from benign tumors and nonneoplastic pathologic involvement of joints, bursae, and tendon sheaths.

The three initial symptoms complained of most frequently were (1)

the presence of a painless mass, (2) the presence of a painful mass, (3) pain and no mass or after a variable time, the presence of a tumor

PAINLESS MASS

Thirty five patients (58.4 per cent) complained of a painless mass as the initial symptom. The insidious nature of the onset and the usual slow growth for a rather prolonged time were characteristic. The mass is usually small averaging about 3–6 cm. in diameter when first observed by the physician, and as a rule is well delineated but not freely movable. Occasionally the tumefaction may be diffuse especially near a joint, and a secondary hydroarthrosis may occur The benign clinical appearance results in an undue delay before the patients present themselves for treatment. Thus among the 35 patients for whom the initial complaint was the presence of a painless mass, the average delay from the onset of symptoms until the institution of adequate treatment was 2.4 years.

The growth characteristics of the tumefactions may develop along one of three different routes

1 They may remain stationary for many years before rapid growth occurs
2. They may continue to grow slowly from their inception.
3 They may grow very rapidly and metastasize relatively early Two patients presented themselves three months after the onset of the tumor and were dead one year later from generalized metastases

PAINFUL AND TENDER MASS

This symptom was observed by 13 patients (21 6 per cent) the majority of whom sought early medical attention The average delay from onset of symptoms until adequate therapy was instituted was 7 8 months In one patient a delay of 6 years resulted when her local doctor advised that nothing was wrong when she first presented herself for treatment.

PAIN

Pain without the presence of a mass or the development of a mass after a variable period subsequent to the onset of pain was mentioned by eleven patients (18.3 per cent) The average delay from onset of symptoms until adequate therapy was instituted was 2.7 years There was nothing characteristic about the nature of the pain to associate it with a malignant neoplasm The patient usually gave a history of vague pains which gradually became persistent and were of a dull character and not localized. Gradually the pain became more intense and localized, usually about a joint, and sharp radiating pain developed, frequently associated with weight bearing A mistaken diagnosis of arthritis was usually made Locking of a joint was never observed in this series. At various intervals following the onset of pain, a tumor mass developed which generally focused attention upon the true diagnosis Pain was most commonly associated with tumors arising from the lower extremity especially those about the knee joint. In one instance a malignant synovioma of the scapular region heralded its presence by initial pain in the hand and wrist, which resulted from pressure on the brachial plexus and the first objective sign of tumor was metastasis in the axilla. Pain is a much more common accompaniment of recurrent sarcoma and may herald the presence of residual tumor long before a mass is detectable

Limitation of joint function seldom occurs early in the history of any individual tumor but occasionally it is the first sign of the synovioma. It sometimes



FIG 332 Roentgenogram of a synovial sarcoma involving the wrist Note the dense appearance of the tumor and the manner in which it compresses the contiguous carpal bones

precipitates an accident which leads to the detection of the tumor

DURATION OF SYMPTOMS

The duration of symptoms of all patients in this series from onset until adequate therapy was instituted averaged 22 8 months, perhaps the longest period of culpability for delay in treatment of any malignant tumor

ROENTGENOGRAPHIC APPEARANCE

Thirty-three of the patients in this series had radiographic studies acceptable for review Robert Sherman and Florence C. H Chu studied these roentgenograms and arrived at the following conclusions concerning the radiographic features of this tumor The malignant synovioma was usually close enough to a joint to be considered possibly in contact with the capsule Narrowing of the joint space indicative of destruction of cartilage was not visualized Joint effusion attributable to the synovioma was detected with accuracy only in the knee joint Osteoporosis was common but not pronounced, it was evident in 10 of the 33 cases studied Periosteal reaction was seen only once and then in association with bone destruction In 4 of the 33 cases, ragged, ill-defined foci of the bone erosion were demonstrated The internal radiographic pattern was that of a homogeneous, structureless mass of water density, with regular margins and without septa

In summary, therefore, one may conclude that there were no characteristic roentgenographic appearances for synovial sarcomas in this series The usual finding was a soft-tissue density usually, but not necessarily, in the vicinity of a joint Calcification may be present occasionally, but in this series it was not observed frequently enough to distinguish malignant synovioma from other soft-tissue densities, although Lewis has stressed the importance of calcific deposits in roentgenograms as a distinguishing characteristic of synovial sarcomas The bones adjacent to the tumor may appear normal or be distorted by pressure, or they may be infiltrated by the primary neoplasm or its metastases Synovial sarcomas, when they invade bone, produce an osteolytic lesion which is not characteristic Knox believes that, in certain instances, joint tuberculosis may be simulated radiographically, and De Santo is of the opinion that pneumoarthrography may be of aid in the x-ray diagnosis of synovial sarcoma

DIAGNOSIS

It is extremely difficult to establish the diagnosis of synovial sarcoma by any means except microscopic examination of the suspected tissue Any subcutane-

ous or deeper tumor of the extremities, especially about the knees the hands and the feet, might be a synovial sar coma The usual small size, insidious onset, indolent growth, and asymptomatic nature lull suspicion away from the very malignant character of the lesion. The occasional sarcoma that arises from synovium and exists as a small, apparently benign mass for many years (10 and 30 years in this series) directs attention to the fact that all soft somatic tumors of the extremities should be held in suspicion as being malignant synovi oma or some precursor of synovial sar coma. It is not possible from these data to remark on the nature of the histology of those tumors of long standing before their malignant characteristics become manifest. In other instances joint pain, usually of a dull, nagging type, aggra vated by effort but seldom interfering with joint motion, may be the signal symptom of a deep-seated synovial sarcoma.

Roentgenograms of the suspicious region may reveal a soft tissue density This is valuable in deep-seated lesions, for it serves to direct the surgeon to the site for biopsy If the soft-tissue density reveals calcific deposits, the suspicion of synovioma is augmented. In those in stances in which bone destruction occurs adjacent to a soft-tissue density the malignant nature of the neoplasm is more certain. Parosteal neurosarcomas and hemangiomas create the same type of bone defect. A diagnosis of synovial sarcoma cannot be made definitely or ruled out absolutely by roentgenologic evidence alone The exact diagnosis must be established always by biopsy

It is important that facilities be avail able for definitive therapy as quickly as possible after the taking of a biopsy The observation that no patient in this series lived five years after a surgical biopsy had been attempted at a variable period before the patient was referred to this hospital emphasizes this statement. (See Chap 7 for technics of biopsy)



Fig 333. Synovial sarcoma. Photomicrograph of a specimen obtained by aspiration biopsy which permitted the histologic diagnosis of synovial sarcoma.

DIFFERENTIAL DIAGNOSIS

Synovial sarcoma must be differenti ated from certain benign tumors other malignant tumors and various nonneoplastic involvements of joints tendon sheaths and bursae

Benign Tumors

Chondroma and osteoma are usually harder and more prone to be attached to bone. Lipomas are of softer consist ence. They are radiolucent. Xanthoma may offer difficulty in the differential diagnosis, but small xanthomas usually involve the flexor tendon sheath of fingers the blood reveals an absolute increase in its lipids or an alteration of the ratio of cholesterol to cholesterol esters.

Other Malignant Tumors

Carcinomas affect the skin Fibrosar comas usually occur in older age groups

(the average age in Warren's group was 50 years) Other malignant neoplasms which must be differentiated include rhabdomyosarcoma, liposarcoma (most frequent in the retroperitoneal, axillary, and inguinal regions), angiosarcoma, melanosarcoma, and schwannoma

RECURRENCE RATE

Synovial sarcomas are notorious for the high incidence of recurrence which develops subsequent to initial attempts at extirpating the neoplasm Of the 60 patients observed at this clinic, primary recurrence developed in 38 following initial attempts at local resection. This value includes all attempts to excise the tumors, including efforts by private doctors as office procedures It does not include amputations A recurrence rate of 63 3 per cent emphasizes the futility of attempting the excision except under most favorable hospital conditions, where good pathologic consultation is available and one is prepared to perform the most radical surgery if indicated That in 8 of these patients the recurrence was noted within one month following excision emphasizes the fact that the excision was incomplete and that surgical trauma may have increased the growth rate The average time for the recurrence to develop following initial treatment was 15 3 months Sixteen patients (26 6 per cent of the series) developed a secondary recurrence an average of 11 2 months following treatment of the primary recurrence There were 5 instances of a third recurrence and a single case in which a fourth recurrence was observed (Table 60)

TABLE 60 SYNOVIAL SARCOMA RECURRENCE RATE

(Authors' Series)

Total number of patients	60
Number who developed a recurrence	38
Percentage of all who developed a recurrence	63 3%
Duration in months from treatment until development of recurrence (average)	15 3
Number who developed a second recurrence	16
Percentage of all who developed a second recurrence	26 6%
Percentage of those who developed one recurrence, then developed a secondary recurrence	42 1%
Duration in months from primary to secondary recurrence (average)	11 2

PROGNOSIS

Although the over-all end results from the treatment of synovial sarcomas are not good, nevertheless cures *are* being achieved Analysis of the data from this series suggests that a higher cure rate could be obtained if the diagnosis be established as soon after the onset of symptoms as possible and proper therapy be instituted immediately The data of this series are accordingly analyzed to note those factors which influenced the five-year-cure rate The time that the patients were treated by us is used as the baseline for computing survival periods

Influence of Age on Prognosis

It is observed in Table 61 that the survival rate is higher in the younger

TABLE 61 SYNOVIAL SARCOMA INFLUENCE OF AGE ON THE FIVE-YEAR SURVIVAL RATE

Age in Years	*Number of Patients*	*Number of Five-year Cures*	*Percentage of Five-year Cures*
Under 20	4	2	50
20–29	12	3	25
30–39	10	2	20
40–49	8	2	25
50–59	3	0	0
60–69	4	0	0
70	1	0	0

age groups. Those patients under 20 years of age enjoyed the highest survival incidence. No patient over 50 years of age in this series survived five years. In the 4 patients under 20 years of age the survival rate was 50 per cent. Of the 34 patients under 50 years of age, the five-year survival rate was 26.5 per cent.

Influence of Sex on Prognosis

Females apparently enjoyed a higher incidence of five-year cures. Six of the nine patients who were apparently free of disease five years after therapy were females.

Influence of Location of Tumor on Prognosis

Table 62 reveals that five-year cures were most numerous in those patients

Table 62. Influence of Location of Synovial Sarcoma on the Five-year Survival Rate

Location	*Number of Patients*	*Number of Five-year Cures*	*Percentage of Five-year Cures*
Lower extremity	23	5	21.7
Thigh (including groin and buttock)	4	1	25
Knee	11	4	36.3
Ankle	0	0	0
Foot	8	0	0
Upper extremity	18	4	22.2
Shoulder	3	0	0
Elbow	2	0	0
Wrist	4	0	0
Hand	7	2	28.5
Finger	2	2	100

with malignant synoviomas of the fingers. Each of the two patients so treated was apparently cured. Lesions about the popliteal space also offered a fairly good prognosis with a five-year survival rate of 36.3 per cent. Lesions of the thigh, including groin and buttock, offered a 25 per cent survival rate, and those of the hand a 28.5 per cent survival rate.

The five-year survival rate for the 23 patients with involvement of the lower extremity is 21.7 per cent, not significantly different from the 22.2 per cent survival rate of the 18 patients with neoplastic involvement of the upper extremity.

Influence of Symptomatology on Prognosis

Although the patients presented a group of nonspecific symptoms the initial one consisted of (1) a painless mass, (2) pain with no mass or followed at a later date by the presence of a mass or (3) a painful mass. Reference to Table 63 reveals that the best

Table 63. Synovial Sarcoma. Relationship of Initial Symptom to Five-year Survival Rate

Initial Symptom	*Duration in Months from Onset until Treatment*	*Number of Patients*	*Number of Five-year Cures*	*Percentage of Five-year Cures*
Painless mass	31.7	23	3	13
Pain and no mass	47.1	6	1	16.7
Painful mass	7.8	13	5	38.4

prognosis existed for those patients whose initial symptom was the presence of a painful mass (38.4 per cent for five-year survival) while those patients who complained initially of pain with no mass revealed a five-year survival rate of only 16.7 per cent (half that of the previously mentioned group) and those whose in-

itial symptom consisted of a painless mass revealed a prognosis of only one-third of those patients who had a painful mass as the initial symptom

Reference to Table 63 further shows that the group who enjoyed the best prognosis delayed least (7 8 months) from the onset of symptoms until definitive therapy was instituted In each of the other groups, there were delays varying from 31 7 to 47 1 months Pertaining to this feature is the observation *that in those patients whose initial symptom* was the presence of a painless mass, the culpability for delay lay with the patients who neglected the slowly growing asymptomatic mass for long periods before seeking medical attention On the other hand, the patients who suffered pain as the initial symptôm usually sought medical advice quickly, but the culpability for delay in establishing the correct diagnosis lay usually with the medical profession Of the six patients in this group, one was given injections and one was given some form of light treatment, the doctor advised a third not to worry about it and he did nothing

TABLE 64 SYNOVIAL SARCOMA EFFECT OF TYPE OF TREATMENT ON THE FIVE-YEAR SURVIVAL RATE

Type of Treatment	*Number of Patients Treated*	*Number of Five-year Cures*	*Percentage of Five-year Cures*
Surgery			
Excision	2	0	0
Amputation	8	0	0
Surgical resection and postoperative irradiation	10	4	40
Irradiation followed by surgical resection	4	1	25
Irradiation	14	4*	28 5
No treatment	4	0	0

* Two patients had a local excision performed elsewhere and radiation therapy given by the authors, but no histologic evidence of persistence of tumor was established

INFLUENCE OF TYPE OF TREATMENT ON PROGNOSIS

Until recently reliance was placed usually upon simple excision, either alone or in conjunction with some form of radiation therapy, or upon radiation therapy alone, to treat synovial sarcoma This conservative treatment combined with the fact that an unduly long time had elapsed before therapy was instituted precludes expectations for good results However, analysis of Table 64, in which the type of therapy is analyzed to rate the ability of the different methods to effect a cure, reveals some interesting data

A *Surgery* No cures were obtained with surgery alone (excision and amputation) This, of course, does not imply that surgery, including amputation, is not efficacious but rather that radical surgery has been resorted to in only the most extensive cases One helpful result of this analysis has been our conclusion that radical surgical measures have been applied too late in the past

B *Surgical resection plus postoperative irradiation* The best results in this series were obtained by wide surgical resection followed shortly by postoperative irradiation The radiation therapy consisted usually of high-voltage x-ray treatments (200 to 250 kv) or teleradium with the 4 gm radium-element pack Four of the ten patients so treated (40 per cent) were free of synovioma 5 years subsequent to therapy In one instance excision of the tumor, which was found attached to the phalangeal capsule, was followed by large doses of x-ray therapy, which *eventually* produced atrophy necessitating amputation of the digit, the amputated specimen did not reveal any evidence of tumor

C *Preoperative irradiation* Of 4 patients treated by irradiation followed by

surgical resection one has survived over five years

D *Radiation therapy alone* Rather surprising are the results obtained by irradiation given in this series as the sole source of treatment. Of 14 patients so treated, 4 are considered five-year cures (28.5 per cent) Full credit for effecting the cure cannot be attributed solely to the radiation therapy because in 2 instances the lesion had been locally excised elsewhere and irradiation was instituted by us as a post excision procedure. However in 2 other instances recurrences from incomplete excision performed elsewhere were biopsied, and the presence of sarcoma established

In one case, radiation therapy to the tumor resulted in atrophy of the digits, and two years after irradiation the digits were amputated and no evidence of tumor was noted In another case a recurrence followed local excision of a tumor in the upper thigh and was diagnosed by biopsy as synovial sarcoma. It was treated by x ray therapy which controlled the local cancer but a metastasis in the groin developed eight months later This metastasis was treated by interstitial radon seeds, and the patient is well 10 years subsequent to therapy

These data demonstrate that irradiation may effect a cure of synovial sarcoma in certain instances and reveal that certain neoplasms although radio-resistant, may nevertheless be radio-curable These observations certainly do not indicate that radiation therapy is superior to proper surgical intervention but do reveal that radiation therapy can be decidedly helpful either as an adjunct to surgery or when surgery is contraindicated as a means of attempting a cure Haagensen and Stout condemn the use of x ray therapy and state that they have been unable to find any clear evidence that irradiation is even of palliative value The data of this series vitiate this conclusion of Haagensen and Stout concerning radiation therapy for synovial sarcoma. In Briggs's report of nine cases of synovial sarcoma, five patients were alive, four of whom were treated by local excision followed by x ray therapy (two of them five-year cures)

INFLUENCE OF PREVIOUS TREATMENT ON PROGNOSIS

Of the 42 patients in the series who have been followed for five or more years since therapy only 7 received the initial definitive treatment at the Memorial Hospital. Thirty-one of the patients had received previous treatment, consisting usually of local excision of the neoplasm—generally incomplete, as evidenced by the fact that 9 recurred within *one month* after excision Four had biopsies performed on an average of 17.5 months before coming to this institution Comparison of the different groups in terms of five-year survival reveals that the highest cure rate (28.5 per cent) was obtained in those patients who were treated initially *at this hospital*. Those patients who had therapeutic attempts made elsewhere showed

TABLE 65 SYNOVIAL SARCOMA. INFLUENCE OF PREVIOUS TREATMENT ON PROGNOSIS

Treatment	*Total Number of Patients*	*Number of Five-year Cures*	*Percentage of Five-year Cures*
Initial treatment by the authors	7	2	28 5
Formal incisional biopsy preceded treatment by the authors	4	0	0
Initial treatment elsewhere	31	7	22 5



FIG 334 Synovial sarcoma involving the medial portion of the right foot



FIG 335 Synovial sarcoma, gross specimen following partial amputation (Same patient as Fig 334)

a five-year survival rate of 22 5 per cent There were no cures in the patients who had incisional biopsies of the neoplasm performed at variable periods before admission

TREATMENT

The treatment of synovial sarcoma revolves about one of three major disciplines (1) treatment of the primary lesion when no metastases exist, (2) treatment of the primary lesion when regional metastases are present, and (3) treatment of metastases which appear after the primary lesion has been apparently controlled Unfortunately, many of the synovial sarcomas are first treated conservatively under the erroneous impression that they represent inflammatory disease

A *Synovial sarcoma without metastases* Various therapeutic measures have been utilized (1) external roentgen radiation (superficial and deep), (2) teleradium therapy, (3) interstitial radon irradiation, (4) local surgical excision, (5) amputation of an involved extremity, or (6) some combination of these methods

Although cures have been obtained occasionally with radiation therapy (two cases in this series), it is our opinion that this type of therapy should be reserved only for the unusual case in which the patient refuses surgery or for use in combination with surgical extirpation Adequate surgical resection is the method of choice in the treatment of malignant synoviomas The extensiveness of the resection depends on the extent of the disease and its location When the neoplasm involves a hand or foot and is deep-seated, it is almost always essential that an amputation of the involved member be performed The radical extent of the amputation will be determined by the clinical stage of the neoplasm Only for the most superficial lesion of the hands and feet should wide local excision be attempted As a rule these neoplasms are so intimately adherent to all surrounding structures, including the bones, that local excision is too often followed by recurrence

Malignant synoviomas which involve an articular surface (joint) cannot usually be resected completely by local excision, and here again amputation at a suitable distance proximal to the cancer is indicated For those neoplasms about



Fig. 336 Gross specimen of a diffuse bulky synovial sarcoma involving the hip joint. This synovioma was treated by hemipelvectomy

the shoulder interscapulothoracic amputation may be resorted to and for those about the hip joint, either a hip-joint disarticulation or hemipelvectomy may be the necessary procedure. Each of the above procedures has been performed by the authors in the treatment of synovial sarcoma.

Primary malignant neoplasms of extraarticular synovial tissue may be treated by wide local excision. Lesions arising from tendons may be excised, providing the lesion is localized and the entire tendon from which the tumor arises is resected. Usually however as the tumor grows, other tendons as well as all contiguous structures become incorporated in the mass which precludes the choice of local resection (Fig 336) It is not generally appreciated that synovial sarcomas are capable of spreading along fascial and muscle planes for extraordinary distances beyond the site of origin.

When neoplasms arise from bursae (wrist thighs abdominal wall etc) a wide local excision may be performed For neoplasms of the extremity which arise from bursal linings it is advisable to resect the entire muscle group in which the tumor is growing If wide local excision is attempted, the surgeon should be prepared to perform an amputation if necessary and to forewarn the patient preoperatively In this series secondary amputations performed following an incomplete local excision have not been encouragingly successful in curing the disease.

For those tumors not far distant from lymphatic drainage regions (axillary nodes inguinal nodes etc.) it is advisable to resect the lymph nodes in continuity with the tumor This procedure is indicated even if nodal metastases are not clinically evident, because of the high incidence of metastases to lymph nodes exhibited by malignant synovial neoplasms Hip-joint disarticulation should also be combined with deep iliac lymph node dissection.

We have considered it advisable to give postoperative irradiation whenever malignant synoviomas have been treated by local resection Although these tumors are frequently radio-resistant, the best results of this series were obtained when radiation therapy was administered postoperatively The type of irradiation varies with the depth of the neoplasm More superficial sites may be treated with low voltage rays (140 kv) while the deeper-seated neoplasms should be treated with high-voltage x rays (250 to 1000 kv) Radiation factors used at Memorial Hospital postoperatively for deep-seated lesions are 200 kv ¼ Cu filter 300 r per day the size of



FIG 337 Synovial sarcoma of the left foot which had extended through the skin, producing a bulky, cauliflower-like tumefaction This was treated by a Lisfranc amputation of the foot and the patient remains well 3½ years after operation

the port varying with the size of the lesion, and a total dose of 3000 to 3600 r × 2 administered With the 1000 kv generator, used in the treatment of a more deeply situated lesion, the dose may be 250 to 300 r per day for a total of from 2100 to 3000 r × 2

When the radium-element pack was utilized, treatment consisted of a dose of 8000 mgh daily for five days until 40,000 to 120,000 mgh had been delivered at a radium–skin distance of from 10 to 15 cm., utilizing the 4 gm radium-element pack, with 0 35 mm of platinum and 1 5 mm of brass filter

In those instances in which a local excision had been performed, usually by the family doctor before the patient was referred to a cancer clinic after the malignant nature of the tumor had been discovered, it had been our practice to administer a full course of irradiation to the operative site At present the policy is to perform a wide surgical resection of the previous operative site, and the large number of cases in which residual cancer is found certainly justifies the procedure A review of the literature reveals that relatively few patients have been subjected to radical surgery early in the course of their disease The combination of a small tumor, mild symptoms, and slow growth makes the surgeon reluctant to perform radical surgery, and conservative excisions are performed frequently, despite pleas for radical surgery (De Santo, Knox, and Coley)

B *Primary synovial sarcoma and metastases to regional lymph nodes* An important method of therapy for a situation in which neoplastic involvement of the regional lymph nodes accompanies the primary synovial sarcoma is radical excision of the primary and lymph-node-bearing regions en bloc The method for attempting a cure in those instances in which involvement of the upper portion of the extremities requires such procedures as hip-joint disarticulation or shoulder (interscapulothoracic) disarticulation is to perform a radical groin or lower neck dissection, respectively, associated with the amputation.

Whenever the synovioma is located on an extremity but proximal to the elbow or knee, and axillary or inguinal metastases are present, and whenever the primary tumor is movable and suitable for radical local excision, the ideal treatment would be an excision and dissection in continuity to encompass the primary site, the regional lymph nodes, and the intervening tissues, namely, skin, fat, fascia, and lymphatics It is unlikely, in our opinion, that any malignant tumor will spread through intervening lymphatics and become entirely deposited by embolic transfer into regional nodes without some of the cells becoming enmeshed en route In certain instances, when neoplasms of the hands or feet are associated with lymph-node metastases,

conservative amputation of the involved member followed in ten to twenty days by a radical axillary or groin dissection has been practiced with ultimate failure and disaster because this procedure permits the intervening tissues to remain unmolested and it is only a matter of time until recurrence develops somewhere in the involved extremity The local surgical measures, radical but short of amputation, may be supplemented by radiation therapy however the relative radio-resistance of these tumors is such that irradiation should not be used exclusively if a cure is anticipated.

C *Metastases when the primary neoplasm is controlled* When regional lymph nodes are invaded by malignant synovioma, the treatment of choice, when technically feasible, is radical dissection of the lymph node-bearing region after the manner described above (*i.e.*, in continuity with the primary lesion or in conjunction with amputation. If the synovioma has become fixed to the parietes or has invaded the vessels or the contiguous bones radical amputation must be performed.

Palliative Radiation Therapy

In our experience deep x ray therapy has offered good palliation Symptoms arising from pulmonary metastases have sometimes responded well to a palliative course of x irradiation. In one instance in this series, metastases to the vertebrae received deep x ray therapy with gratifying symptomatic results. Local recurrences usually respond well also to radiation therapy which should be utilized in every case in which operative removal is contraindicated or impossible

CASE REPORT NO 60: SYNOVIAL SARCOMA OF THE THUMB

A 36-year-old white American housewife presented herself and said that as long as she could remember she had had a marble-sized lump at the base of the metacarpal of the left thumb One year before admission it began to increase in size but it had always been painless. Eight months later she had a surgical excision performed elsewhere. Histologic section revealed a synovial sarcoma, probably of tendon sheath origin, which presented characteristics of being locally invasive but not prone to generalized metastases

Following resection the wound did not heal and a central ulceration at the base of the metacarpal of the left thumb at the dorsum of the wrist persisted (Fig 30A) She then presented herself to us for treatment. Because of the failure of the wound to heal, it was believed that underlying recurrence was present and a tumor mass which measured 3¼ × 3½ cm. in diameter and was slightly movable was palpated.

An attempt was made at wide surgical excision, but the tumor was so extensive that amputation of the thumb was necessary (Fig 30B) The resected specimen revealed the tumor extending to the extensor tendon which it partially surrounded, and a diagnosis of the resected specimen was synovioma of a chondrosarcoma type The wound healed well The patient was given a postoperative course of irradiation 200 r daily over the left hand for a total of 2000 r-10 × 15 cm port, 35 cm target–skin distance, 200 kv ½ mm Cu and ½ mm Al filtration, 25 ma.

The patient was well for one year when a small nodule was noted at the middle aspect of the upper portion of the scar It was resected and found to be intimately attached to the ligaments of the carpal bone. The pathologic diagnosis was recurrent synovial sarcoma. The patient was given another course of deep x ray therapy receiving 250 r daily from July 26 to August 8, 1938 for a total of 3000 r 200 kv and 9.3 × 5.4 cm port.

Twelve years after the initial operation the patient developed a metastasis in the lung (Fig 33B) for which a lobectomy was performed, and five years later she was treated for metastases to the scalp by a combination of local surgical excision for some of them and deep x ray therapy for others



FIG 338 Synovial sarcoma Roentgenogram demonstrating a solitary, spherical pulmonary metastasis from a synovial sarcoma of the base of the thumb illustrated in Fig 30 This was removed by lobectomy (Case report No 60)

CASE REPORT NO 61 SYNOVIAL SARCOMA CURED BY LOCAL EXCISION PLUS POSTOPERATIVE IRRADIATION

The patient was a 38-year-old Negro male from Jamaica, British West Indies, a packer for a dress house He presented a history of having noted a lump the size of a filbert over the olecranon process of the right ulna about five years before admission This had gradually and progressively increased in size There had never been pain, discharge, or ulceration Examination revealed a firm, elastic mass measuring 7 × 6 × 5 cm over the extensor surface of the right elbow (Fig 339) The overlying skin was partially fixed to the mass, and several large superficial veins were noted There was no limitation of motion of the elbow joint

X-rays of the right elbow revealed a soft-tissue process in the olecranon region (Fig 340)

On February 24, 1940, a wide surgical dissection of the posterior aspect of the elbow was performed with an apparently complete excision of the tumor mass The tumor appeared well encapsulated seemed



FIG 339 Clinical photograph of a synovial sarcoma involving the right elbow (Case report No 61)

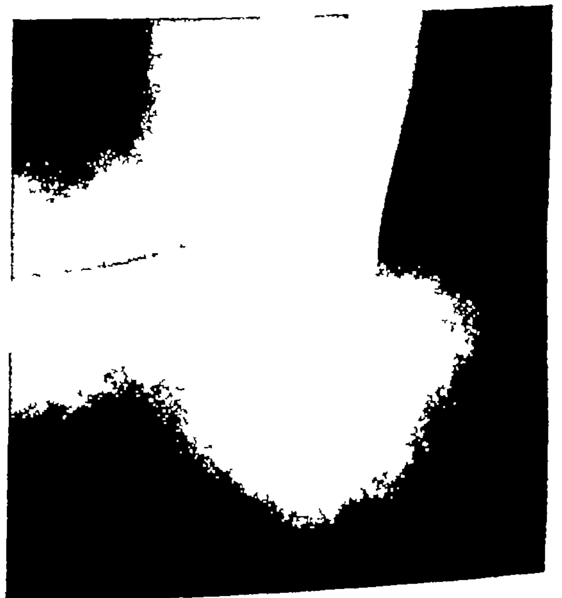


FIG 340 Roentgenogram of synovial sarcoma of the right elbow shown in Fig 339



FIG. 341 Synovial sarcoma. Gross specimen and cut section of the tumor shown in Fig 339 following local excision of the sarcoma.

to arise from the olecranon bursa, and consisted of a large mass which measured 9 0 × 5 5 × 6 0 cm with a fingerlike extension from the main mass behind the triceps muscle for a distance of about 6 cm (Fig 341) The mass was rubbery in consistency and cut section revealed a shiny gelatinous surface of whitish mottling on a light yellowish brown background.

The microscopic report was synovioma *spindle-cell type, of a low grade malignancy* arising from either synovial membrane or an entering tendon or aponeurosis

Irradiation

The patient was *given a postoperative* course of roentgen irradiation daily dose of 250 r for a total of 2000 r from March 25 to April 2, 1940 with the following factors 250 kv 1.5 mm. Cu 50 cm. target–skin distance, 10 cm port 30 ma. Treatments were given over the posterior aspect of the elbow

The patient has remained well without *evidence of recurrence*

END RESULTS

Of the 60 patients of this series, 14 are alive and apparently free of disease an average of 7.5 years after treatment. The end results are tabulated in Table 66 It may be noted that of the 60 patients observed, only 42 were *suitable for* evaluation of five-year survival rates because 18 patients were treated within the past five years Of the 42 patients treated more than five years ago 8 are alive and free of disease over five years *The absolute five year survival rate is 19.1 per cent* Seven of these patients are alive more than ten years after therapy (16 7 per cent)

Of the 42 patients who were treated here over five years ago 3 were lost to follow up One of these patients was a "clinic shopper" who merely came in for an examination and never returned. Two other patients were apparently free of synovioma when lost to follow up one and two years after therapy Since it is not possible to know the final outcome in these patients if they be excluded from the number of cases considered for follow up evaluation, *the relative five year survival rate is 20.5 per cent* In order to adjudge the efficacy of the therapeutic attempts at the hospital and establish a therapeutic five-year survival rate, 5 additional patients are excluded from the calculations These patients received no definitive therapy because when they presented themselves to the clinic they were riddled with

TABLE 66. FIVE-YEAR END RESULTS IN CASES OF SYNOVIAL SARCOMA STUDIED AT MEMORIAL HOSPITAL, NEW YORK

Total number of patients	60
Number used to compute five-year survival	42
(Eighteen patients were treated too recently to be considered in the five-year survival rate)	
Number alive and free of disease five years or more after treatment	8
Absolute five-year survival rate	19 1%
Number of patients lost to follow-up before five-year period	3
One merely came in for an examination and never returned	
One, well for two years, lost to follow-up	
One, well for one year lost to follow-up	
Relative five-year survival rate	20 5%
(Patients lost to follow-up subtracted from total number of patients)	
Number of patients on whom a curative procedure was attempted at Memorial Hospital	37
(Five patients when first observed suffered from extensive pulmonary metastases and either no treatment or palliative radiation therapy was given)	
Number of patients used to compute therapeutic five-year-survival rate	34
(Three patients lost to follow-up and five patients on whom no curative therapy was applied are subtracted from all patients in the series)	
Therapeutic five-year survival rate	23 5%

sarcoma, including diffuse pulmonary metastases Either palliative radiation therapy was administered to the metastases, or no treatment whatsoever was given to these patients Accordingly, of the 42 patients, in only 37 were curative procedures instituted Of these, 3 were lost to follow-up, which leaves a total of 34 patients from whom therapeutic five-year survival values can be determined, *i e*, patients who received definitive therapy and were followed for over five years *The therapeutic five-year survival rate of this series is, accordingly,* 23 5 *per cent*

Although these results are not good, the data demonstrate that cures are being attained even in the presence of prolonged delays and frequently traumatic intervention before definitive and adequate treatment is instituted

These data should dispel the pessimism expressed by Haagensen and Stout when they state that only 3 patients in a group of 104 reported in the world literature (including 9 of their own) were clinically cured for more than five years after treatment Their statement may be misleading, because in the series which they present, the final result was not recorded in 15 instances and 39 additional patients were living after treatment, but sufficient time had not elapsed for computations of five-year survival rates.

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CHAPTER 21

Tumors of Smooth Muscle

LEIOMYOMA

TUMORS of smooth muscle are extremely rare in the soft somatic tissues of the body They are most frequent in the uterus especially the benign leiomyomas but even in this organ malignant tumors are relatively rare. About 1 per cent of all uterine leiomyomas become malignant. Other sites of occurrence are in the gastrointestinal tract. Approximately 67 leiomyomas of the esophagus were reported to 1953, according to Wilder and Moore Approximately 50 per cent of the tumors of smooth muscle origin of the small and large bowel are malignant. Hepatic metastases are present in 30 per cent of the patients Tumors of smooth muscle also occur in the mesentery retroperitoneal space (Fig. 342) orbit, omentum, mediastinum, and broad ligaments

Stout has classified the benign leiomyomas into (1) superficial leiomyomas composed almost entirely of smooth muscle element, which he believes are derived from the smooth muscles of the skin in the genital region, and (2) vascular leiomyomas, which he believes arise from the smooth muscle of the blood vessels These are very vascular and contain many components of smooth



FIG. 342. Retroperitoneal leiomyoma. Gross appearance of a tumor which was successfully resected. (*Courtesy* Dr Gordon McNeer)

muscle as well as tiny blood vessel elements He states that these may occur either as solitary or multiple tumors They rarely grow to large size and may occasionally produce attacks of paroxysmal pain, similar to the pain produced by the glomus tumor. When they are multiple they are not scattered diffusely over the body but tend to be grouped together in a particular region We have seen these vascular leiomyomas only infrequently and believe that our pathologists probably report them as angiomyofibromas or as fibrosing angiomas Stout states that malignant changes in skin leiomyomas have never been known to occur.

LEIOMYOSARCOMA*

In our series of over 700 cases of sarcomas of the soft somatic tissues we have had none which were diagnosed as leiomyosarcomas. Numerous retroperitoneal and visceral leiomyosarcomas have been observed. Stout reports 25 leiomyosarcomas in his entire series, of which seven occurred in the soft somatic tissues He reports that four of these patients have died from blood-borne metastases, which occurred from two to five years after local excision, two patients are well nine years after excision and postoperative irradiation, and one has been lost to follow-up



FIG 343 Leiomyosarcoma The elongated, spindle-shaped cells tend to group themselves in fascicules The blunt nuclei differentiate these cells from those of fibroblastic origin, but special stains are of inestimable value (*Courtesy*, Dr George K Higgins)

The gross pathologic appearance is typical, the neoplasm being brownish-tan in color, with regions of central hemorrhagic necrosis Those which we have observed in the retroperitoneal region had usually grown to large sizes, were not encapsulated, and extended into the contiguous structures to infiltrate the organs in juxtaposition to the tumor Microscopically, the leiomyosarcomas are composed of the typical spindle-shaped type of cell containing reticulum fibers interdigitating in a more or less haphazard arrangement (Fig. 343) Stout states that the cells usually show the intracytoplasmic myofibrils, although at times these may be absent Careful fixation with either Bouin's or Zenker's fluid is necessary to distinguish the myofibrils Stout believes that if one or more mitoses are present in the high-power field, the tumor is malignant and he further calls attention to the fact that an apparently differentiated leiomyoma without mitoses may metastasize

Irradiation has little effect upon these tumors and the only treatment is similar to that of other sarcomas, namely, careful and bold surgical attack

* Exclusive of leiomyosarcoma of viscera

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CHAPTER 22

Tumors of Striated Skeletal Muscle[*]

INTRODUCTION

HISTORIC NOTE

TUMORS of striated muscle have been recognized since 1854 when C O Weber, writing in Virchow's Archives, described a tumor in the tongue of a 21-year-old man The tumor was surgically excised but recurred On histologic examination the tumor was composed of striated-muscle cells showing all stages of development from embryonal to adult cellular structures Other ancient case reports in the literature, not all of which are verified, were by Billroth (1856), Buhl (two cases, 1865), Ribbert (two cases, 1891), and Bayer (orbit of a child, 1882) Their occurrence has been described in fish, birds, rats, and mice

In 1943 Nettleship, in the Journal of the National Cancer Institute, described a spontaneous transplantable mature type of rhabdomyosarcoma in Strain C mice This tumor was similar to such tumors in man but contained more adult-type cells with intact cross-striations and myofibrils In earlier years arguments waged that true muscle tumors did not occur and that such neoplasms actually originated from the connective-tissue septa within the muscle bundles, but now, with selective staining and more exact histologic criteria, there is, of course, incontestable proof that rhabdomyogenic tumors do exist The experience of any one physician or institution with this rare neoplasm has been so limited that little has been described about its natural history or behavior

NOMENCLATURE OF STRIATED-MUSCLE TUMORS

The chance location of the tumor within the muscle bundles, and even invasion of muscles by the sarcoma, has led to the improper inclusion of a large group of tumors under the classification of *sarcomas of skeletal muscle.* The title under these circumstances is a misnomer as it refers only to the location of the tumor within the muscle and not to its histogenesis, on which the proper nomenclature should be based

Rakov prefers the term *malignant rhabdomyoblastoma* because it applies to tumors consisting of immature striated-muscle cells which show infiltrative destructive growth and a capacity to metastasize He has rejected the terms *myosarcoma* and *rhabdomyosarcoma* as

* In collaboration with Warren F Eberhart

TABLE 67 MALIGNANT TUMORS OF THE SOFT SOMATIC TISSUES

Histologic Type of Tumor	*Number*	*Percentage*
Total cases	717	100 0
Sarcoma of undetermined histogenesis	261	36 4
Liposarcoma	105	14 6
Rhabdomyosarcoma	100	13 9
Synovioma	60	8 4
Kaposi s sarcoma	48	6 7
Malignant neurilemmoma	46	6 4
Fibrosarcoma	39	5 4
Dermatofibrosarcoma protuberans	39	5 4
Angiosarcoma	19	2 6

unsuitable because they imply incorrectly an origin from mature striated muscle cells. The authors conception of the usage of these various terms is adumbrated in the accompanying classification.

CLASSIFICATION OF TUMORS OF STRIATED MUSCLE

No classification of these tumors can be made which is entirely satisfactory The student of muscle tumors is indebted to Abrikossoff Cappell, and Montgomery but especially to Arthur Purdy Stout, for contributions elucidating the various categories A clinical as well as histologic grouping is necessary for the understanding of the neoplasms.

A *Nonmyoblastic tumors involving skeletal muscles* These are of clinical interest because of the difficulties of differential diagnosis and the similarity of indications and plans for treatment.

1 Sarcomas originating within the gross muscle bundles from connective tissue or stromal elements such as the perimysium, the interfascicular connective tissue, and the perineural or perivascular connective tissue Sarcomas developing in myositis ossificans would be a classic example

2. Sarcomas developing without the muscle but invading it secondarily and by continuity e g., parosteal bone sarcomas, fibrosarcomas and malignant neurilemmomas

3 Sarcomas metastatic to muscles from distant sites e g malignant synoviomas and liposarcomas

B *True myoblastic tumors of skeletal and other striated muscles* The striated muscle cell is certainly not a common component of tumors considering the vast number of neoplasms which occur in humans, but it is found in full or complete differentiation in the following instances

1 Teratomas and mixed-cell tumors of various organs such as the testis kidney ovary and prostate. Some of the best opportunities to study the well-differentiated striated muscle tumor cell is in the moiety of the malignant mixed tumors examples of which are the sarcoma botryoides of the uterovaginal canal and the Wilms s embryonal adenomyosarcoma of the kidney

2. Congenital myoblastomas of the tongue and of the cardiac muscle These latter muscle tumors and neoplasticlike tumefactions of the heart are sometimes associated with other abnormalities such as tuberous sclerosis

3. Malignant myoblastic tumors of skeletal muscle. These neoplasms comprise the body of this report and constitute the *only group involved* in the statistical analyses. Abrikossoff in 1926 and later in 1931, subdivided these neoplasms of skeletal muscle into four histologic groups which are probably not different types but represent degrees of differentiation of these tumors He described the round

oval, or elongated mononuclear cells, 20 to 26 microns long, occurring in bundles, possessing granular acidophilic cytoplasm and with or without longitudinal or cross striations

(a) Pure myoblastomas, composed of myoblasts without striations These cells morphologically and tinctorially resemble skeletal muscle cells

(b) Myoblastoma, with similar cells except that longitudinal or cross striations or both may be found imperfectly developed in the periphery of the tumor cell

(c) Rhabdomyosarcoma, with hypertrophic myoblasts, some enormous (40 to 150 microns long), frequently multinucleated and syncytial, with occasional striations

(d) Rhabdomyosarcoma, with atypical myoblasts, anaplastic, polymorphic celled, with regions of high differentiation showing longitudinal and cross striations.

BENIGN TUMORS OF STRIATED MUSCLE

RHABDOMYOMA

An occasional tumor composed of well-differentiated myoblasts has been described as occurring in the tongue, striated muscles, and the heart. Whether or not these descriptions refer to a distinct tumor entity, rhabdomyoma, or if they are granular-cell myoblastomas (tongue) or unique tumors of the heart (see below) awaits elucidation At any rate, those described as rhabdomyomas are localized tumors of limited growth potential, do not metastasize, and are cured by local excision

MYOBLASTOMA OF ABRIKOSSOFF

In 1926 Abrikossoff described five patients with a peculiar muscle tumor which he termed *myoblastic myoma* Three tumors were located in the tongue, one on the upper lip, and one on the leg The cells of these tumors were believed to arise from the embryonal ancestors of voluntary muscle The tumors occur more commonly in the third and fourth decades of life, a few have been described as congenital in origin The granular-cell myoblastomas have unusual distribution, occurring more commonly in the tongue, the lip, vocal cords, esophagus, and breasts. In a review of granular-cell myoblastoma, Howe and Warren (1944) collected 158 cases from the literature to which they added 10 of their own Fifty-six per cent of the tumors in their series occurred in the upper respiratory and digestive tracts Fifty-nine cases, or more than a third, occurred in the tongue, which appears to be the most common site for muscle tumors of this type (Fig 344). In the tongue the tumor is usually situated on the dorsal aspect or near the base, and is firm, discrete, yellowish or greyish-white on transection Although the majority of the tumors are well demarcated and pseudoencapsulated, a few are infiltrative and ill defined in their margins Myoblastomas occurring in the upper digestive or respiratory tract are usually found immediately beneath the mucous membranes as submucosal swellings.

Since the initial description of the granular-cell myoblastoma by Abrikossoff, this tumor has been generally accepted as one composed of immature myoblasts Howe and Warren believe these tumors should be segregated as a group, separate from the rhabdomyomas and rhabdomyosarcomas

Abrikossoff separated myoblastomas

into four types, depending on the cellular structures (1) pure myoblastomas, composed of myoblasts, completely devoid of striations (2) tumors with myoblasts as in type No 1 but with imperfectly developed longitudinal or cross striations in the margins of the cells (3) tumors composed of hypertrophic myoblasts Some of these cells attain great size up to 160 microns in length. They are frequently multinuclear and of the syncytial type. Peripheral striations may or may not be present. (4) Atypical myoblastic sarcoma. This is a polymorphous cell tumor In some areas it is frankly sarcomatous in others it is highly differentiated, with well-defined cross striations Howe and Warren believe the tumors in this group to be really rhabdomyosarcomas

The characteristic cell of the myoblastoma is a large, pale, polyhedral shaped cell with acidophilic cytoplasm, which is occasionally vacuolated. These granular-cell myoblastomas in the oral cavity give the initial microscopic impression of xanthoma, because the large vacuolated cells in a myoblastoma are readily confused with the foam cells of xanthoma. Masson's trichrome stain is employed for differentiation inasmuch as the myoblasts and myofibrils stain red in contrast to the green connective-tissue fibers

The granular-cell myoblastomas are generally benign tumors Howe and Warren reported only 11 per cent of their total series to be malignant, and of these only 3 had definitely metastasized The common manifestation of malignancy when this rare complication does occur seems to be local invasion and recurrence after simple excision rather than dissemination by lymphatic or blood stream permeation. Howe and Warren urge that myoblastomas of this type be treated as malignant tumors if there is cellular atypism, excessive mitotic figures, spindle-cell or sarcomatous pattern and structure, or local invasion.



FIG. 344. Benign granular myoblastoma of the tongue. (Case report No. 62.) (Pack and Eberhart, Surgery 32 1023 1952.)

The treatment of preference is wide surgical excision.

RHABDOMYOGENIC TUMORS OF THE HEART

Von Recklinghausen in 1862 first reported a congenital rhabdomyoma of the heart. This tumor occurs most often in the newborn and children. In a review of the literature, LaBate collected 51 cases of which 46 occurred in patients younger than 15 years In data presented by Batchelor and Maun, 52 per cent of the patients died in the first year of life and 86 per cent before the age of puberty The rhabdomyoma of the heart occurs with equal frequency in the sexes and has been reported in Negroes and Japanese as well as Caucasians. This tumor is almost always associated with some other congenital anomaly such as harelip cleft palate, cystic kidneys sebaceous adenomas malformations of the pancreas and, most frequently of all, tuberous sclerosis of the brain (50–60 per cent according to Ponfick)

Antemortem diagnosis is seldom made because the clinical symptoms are nonspecific Cardiac arrhythmias, disturbances of the conductive system of the heart, cyanosis, and detectable murmurs are noted if the tumors involve the valvular leaflets Epileptiform seizures and other symptoms referable to the central nervous system might be anticipated in view of the commonly associated tuberous sclerosis

The rhabdomyoma of the heart is a benign lesion, and malignant transformation has not been recorded Batchelor and Maun have suggested that the term *congenital nodular glycogenic tumor of the heart* should replace the term *congenital rhabdomyoma* Steinbiss contends that these lesions should not be designated nor regarded as true neoplasms, because they do not exhibit proliferative activity, and degenerative changes such as fibrosis and calcification have been observed in the older lesions Farber also considers the disease to be a malformation rather than a true tumor The diffuse type of rhabdomyomatosis of the heart has been considered a form of Gierke's glycogen storage disease Monckeberg demonstrated glycogen in the tumor cells Wolbach, employing phosphotungstic acid-hematoxylin stain, demonstrated beginning muscle fibrillae formation, which influenced him to label the rhabdomyoma a true neoplasm Abrikossoff, Monckeberg, Knox, and Schorer were of the opinion that the tumor cells originate from the Purkinje fibers, but Steinbiss, Amersbach, and Handorn claimed that the tumors are found most often where the conduction system could not be demonstrated Von Recklinghausen, Seiffert, Ponfick, and others have recognized a similar appearance of these tumor cells to the embryonic heart muscle cells

These tumors of the heart, of disputed character, may be subepicardial, intramural, or subendocardial and may occur in any part of the heart, including the valves, but more often arise in the left ventricle They may be single or multiple and appear as discrete or diffuse white, soft, homogeneous foci The interlacing bundles of cardiac muscle fibers are distended and infiltrated by the tumor tissue Under the microscope the so-called spider cells are many-processed cells lying within vacuolated regions Some histologists consider these highly characteristic spider cells as huge embryonic cells, but Batchelor and Maun assert that the spider cell "represents a striated muscle cell that has become vacuolated by intracellular accumulations of glycogen in such a manner that the nucleus of the cell remains centrally located surrounded by a narrow zone of cytoplasm while the remaining cytoplasm assumes a spider web pattern"

RHABDOMYOMATOUS TUMORS OF THE URINARY BLADDER AND PROSTATE

In lower animals the urinary bladder is one of the most frequent sites of visceral rhabdomyomatous tumors Cappell and Montgomery have described two distinct forms of striped-muscle tumors of the urinary bladder The more frequent type is a polypoid tumor with bulbous processes suspended from a common stalk and analogous in its gross and perhaps embryologic relationships to the vaginal sarcoma botryoides. Both longitudinal and cross striations are present in the muscle cells, which may be of the strap-cell type or large cells with vacuolated cytoplasm resembling spider cells The second variety is a mushroom-shaped tumor with broad stalks which Cappell and Montgomery have found to originate usually from the bladder trigone

The origin of rhabdomyomatous tumors of the urinary bladder and prostate is uncertain, but the theory is that they may have arisen from displaced myotomes associated with descent of the

Wolffian duct Striated muscle tissue is present in the *posterosuperior* portion of the prostate gland of the fetus and in *children*, *presumably* it is from this site that the rhabdomyomatous tumors of the prostate develop in later life.

MYOBLASTOMAS OF THE SPERMATIC CORD AND GUBERNACULUM

These rare muscle tumors are seldom mentioned in medical literature we have contributed two case reports of this unusual occurrence, one benign and one malignant (case reports Nos 65 and 66) The genesis of primary rhabdomyomas of the spermatic cord is uncertain Stoerck and Monckberg independently observed instances in which the neoplasms arose in the vas deferens. Hirsch reported this occurrence in the gubernaculum testis Inasmuch as these structures are composed of smooth muscle fibers the neoplasms would naturally be expected to contain unstriped muscle cells, but this supposition is not always true as the cells occasionally may exhibit cross striations

MALIGNANT TUMORS OF STRIATED MUSCLE —RHABDOMYOSARCOMA

In a twenty year period, 100 cases of striated muscle sarcoma have been seen at the Memorial Cancer Center and the Pack Medical Group The statistical data reviewed in this study are based solely on the tumors of skeletal muscle, because the inclusion of visceral, lingual, and cardiac muscle tumors confuses the conclusions drawn about methods and end results of treatment.

INCIDENCE

Considering the enormous amount of *voluntary muscle which comprises the* human body the incidence of muscle tumors is amazingly low On the basis of relative weights per pound of human flesh, skeletal muscle has fewer tumors than any other tissue There is practically no information in medical literature concerning the incidence of this tumor but it must be a very rare neoplasm The rarity of rhabdomyosarcomas must be due to the fact that striated muscle cells are completely differentiated and do not undergo cellular division in postnatal life as do the cells in skin, bone breast and the mucosas

At the *Oncological Institute* in Leningrad 20 per cent (17 cases) of the sarcomas of soft somatic tissues treated between the years 1926–1934 were rhabdomyosarcomas The 100 striated muscle sarcomas comprising our report represented 13 9 per cent of our 717 sarcomas of soft somatic tissues so that it is a rare histogenetic type in a scarce group of malignant tumors (Table 67)

AGE AND SEX DISTRIBUTION

For some unexplained reason the rhabdomyosarcomas occur with somewhat greater frequency in males, *e.g* 61 males and 39 females (Pack and Eberhart) 62 males and 52 females (Stout)

Rhabdomyosarcomas occur at all ages from early infancy to extreme old age This tumor was found *predominantly* in middle and older age groups with 65 per cent in the 40 to 70 year age bracket and the highest incidence in the sixth decade (28 per cent) Our oldest patient was 78 years, and the youngest was only 5 weeks old Moulonguet and Pollosson have commented on a supposed relative immunity of children to this tumor however four patients in our report were under 10 years of age, of whom one has been cured for 13 years. Since this statistical analysis was completed, two more children of 5 years

TABLE 68 RHABDOMYOSARCOMA OF SKELETAL MUSCLES AGE OF PATIENTS

	All Cases		*Determinate Cases*		*Five-year Cures*	
Age of Patient	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Total cases	100	100 0	65	100 0	22	100 0
10 years and less	4	4 0	2	3 1	1	4 5
11–20 years	2	2 0	2	3 1	2	9 1
21–30 years	8	8 0	5	7 7	3	13 6
31–40 years	9	9 0	5	7 7	4	18 2
41–50 years	20	20 0	14	21 5	2	9 1
51–60 years	28	28 0	20	30 8	7	31 8
61–70 years	20	20 0	10	15 4	3	13 6
71 years and over	9	9 0	7	10 7	0	0 0

of age had radical local dissections of rhabdomyosarcomas of the extremities

ETIOLOGIC FACTORS

The malignant tumors of striated muscle, or rhabdomyosarcomas, may originate from preexisting benign myomas, but in the majority of instances seem to develop *de novo* There is paucity of theories to explain the genesis of this tumor, and none of them appears tenable except, perhaps, the congenital one The striated-muscle cell is a completely differentiated end product and, according to embryologists, is capable of enlargement but not of cell division in postnatal life The repair of muscle is by fibrous-tissue replacement and not by regrowth of new muscle cells Furthermore, the best opportunity to study striated-muscle neoplasia is the myogenic compound of teratomas and mixed-cell tumors, admittedly of congenital origin There is no evidence to indicate that postnatal influences contribute to the genesis of rhabdomyosarcomas

Trauma plays no role in the causation of the rhabdomyosarcomas, but the limb or part containing the tumor is more predisposed to injury, in fact, treatment has often been delayed due to a presumptive and incorrect diagnosis of charley horse Seven patients were able to recall some type of trauma to the approximate location in the body where a muscle tumor subsequently developed When we consider the number of bruised arms and shins which fall to the lot of the average individual, it seems safe to disregard trauma as an etiologic factor

EMBRYOLOGIC RELATIONSHIP OF STRIATED-MUSCLE TUMORS

Keith has declared that no new fibers are formed in skeletal muscles after birth, the growth of muscles in bulk being effected solely by enlargement of the previously existing cells Tissue so well differentiated as striated muscle would not ordinarily be expected to participate in tumor growth *de novo* in mature life The relative frequency of rhabdomyosarcomatous tumors in childhood, even of congenital origin, lends support to the theory that the genesis of many striated-muscle tumors *may* be from prenatal life Tumors composed of muscle fibers as the chief component may originate in the known groups of striated muscles or in remote regions wherein they are perhaps embryonal misplants

Geschickter summarized the development of muscle tissue as follows. With in the first month of embryonic life, the mesoderm spreads out from the hind

end of the embryo and separates into a paraxial mass, an intermediate cell mass and sheets applied to the body wall and primitive digestive tube. In the paraxial mesoderm and in the primitive body wall the segmental voluntary muscles are developed. In the intermediate cell mass, the musculature connected with the urogenital organs develops and in association with the splanchnopleure, applied to the primitive gut, the muscles of the digestive tube, the heart and the large blood vessels develop"

Cappell and Montgomery have described the pattern of histologic evolution of the striated muscle cells as follows "*In its development, the voluntary muscle passes from a syncytial stage in the mesenchyme to a myoblastic stage and subsequently to a myofibrillar stage in which the developing muscle fibers show a beading effect followed by the appearance of cross striations.* The primitive muscle cells or myoblasts are at first round and oval but rapidly become spindle-shaped while at first retaining their mononuclear structure. The spindle cells later elongate and their nuclei show mitotic divisions without separation of the cytoplasm so that by the second month of embryonic life, multinucleated syncytial strands are formed, in the peripheral zone of which longitudinal fibrils appear while at the same time, the central zone remains undifferentiated and contains the nuclei of the muscle fiber Later as the fibrillation spreads to the center of the cell, the nuclei then migrate to the outer cytoplasmic layer where they arrange themselves around a zone of clear sarcoplasm, from which the sarcolemma is later derived. They find that transverse *striations appear only later after the fibrillation is well advanced*"

GROSS PATHOLOGIC ANATOMY

The gross appearance of the tumor exhibits considerable variation. It may

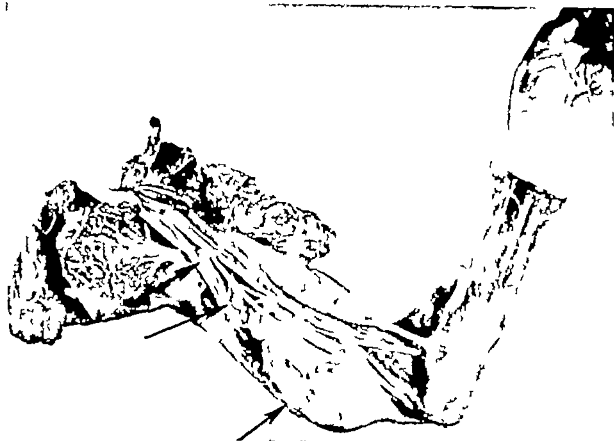


Fig 315 Recurrent rhabdomyosarcoma. Note multiple tumor foci (arrows) a frequent cause of recurrence

be single, multilobulated, or even multicentric with separate discrete tumors comprising the pattern of tumor genesis The neoplasm may be discrete and encapsulated or so diffuse in its extent that its identity as a tumor may be questionable at first The tumor nodule may be flattened within the muscle sheaths Although in gross appearance the tumors appear to be encapsulated or infiltrating, it would be better to consider the tumor as circumscribed rather than encapsulated because, in truth, the appearance of encapsulation is an illusion, the neoplasm does extend far beyond the edge of the circumscribed growth The disparate appearance of these two types is due to the manner of growth of the lesion, namely, by expansion in which the appearance of cir-



Fig 3-16 (*Upper left*) Congenital rhabdomyosarcoma of the lower leg (Pack and Eberhart, Surgery 32 1023, 1952) (*Upper right*) Clinical appearance shortly after dissection of the tumor in figure on left No evidence of recurrence 4 years later (*Lower*) Gross specimen, the result of wide surgical dissection of the tumor with preservation of the extremity

cumscription follows or by infiltration which is characteristic of the diffuse manner of growth

Gordon Taylor has stated this point of view succinctly as follows "The distinction between the two groups is perhaps of academic rather than of clinical or therapeutic value, nor should the pathological anatomical classification into infiltrating and encapsulated forms be labored too zealously for these tumors have no true capsule and the abolition of the word, encapsulation is better calculated to relegate the operation of so-called enucleation for these tumors in the background"

There is great variation in the degree of hardness depending upon the collagen content the connective-tissue component of these tumors differs greatly in quantity The softness also depends in part, on the degree of vascularity the existence of myxomatous changes, and the presence or absence of degeneration with cystic formation. Sometimes the tumor is quite soft and presents a mottled, greyish, yellow red appearance on cut-section. The lobulations appear outlined by connective tissue septa. Cystic cavitation may be the result of degeneration necrosis or hemorrhage with absorption Hemorrhagic necrosis may be massive and give the lesion the appearance of a large hematoma.

Hemorrhagic Rhabdomyosarcoma

Extensive intratumoral hemorrhage can and does occur within soft tissue sarcomas more commonly in the rhabdomyosarcoma. The hemorrhagic necrosis is so massive that it resembles in this way the peculiarity of telangiectatic osteogenic sarcoma (the so-called malignant bone aneurysm) There is an extensive fluidlike spread along the fascial planes The lesion bears a clinical resemblance to a large hematoma. On sectioning the fluctuant mass, a gush of fluid blood occurs with extrusion of tumor substance, leaving large cavities lined by fibrin and occasional tumor tissue. The quantity of intramural hemorrhage contributes to a marked anemia Two surgical difficulties are encountered in the removal of such a tumor one, the hazard of excision without rupturing the tumor and causing spillage into the operative wound and, two, the amputation or dissection must be well above the superior limit of extravasated tumor tissue along the fascial planes The prognosis is grave under these circumstances because of the frequency of pulmonary metastasis





FIG. 347 (*Upper*) Gross specimen of rhabdomyosarcoma arising from left biceps in a 30-year-old female treated by wide local excision. Patient without evidence 13 years after surgical extirpation. (*Lower*) Gross specimen of rhabdomyosarcoma arising from left thigh in a 45-year-old male who succumbed from pulmonary metastases one year after excision



Fig. 348 Rhabdomyosarcoma of the biceps muscle The level of amputation is above the origin of the involved muscle, namely, an interscapulothoracic amputation (Pack and Eberhart, Surgery 32 1023, 1952)

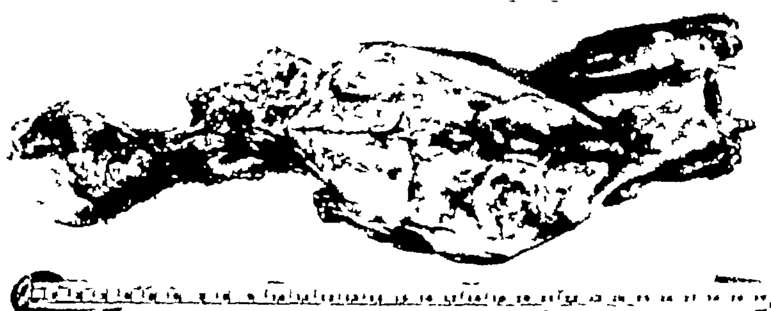


Fig 349 Dissected gross specimen of rhabdomyosarcoma (amputation) Note smooth, homogeneous structure with small intratumoral hemorrhages, seen on cross-section (Pack and Eberhart, Surgery 32 1023, 1952)

Multicentric Origin

The multiplicity of these tumor nodules, each discrete and separate, has not been generally appreciated by pathologists and surgeons We have encountered identical smaller tumors in adjacent muscle, although preoperatively only the major lesion was detected This has led us to conclude that the rhabdomyosarcoma is occasionally multicentric in origin and offers the logical reason why the radical dissection should include a removal of the entire muscle in which the tumor develops and even the group of muscles, if more than one are involved by the multicentric tumor process (Fig 345)

HISTOPATHOLOGIC FEATURES OF RHABDOMYOSARCOMA

It is very likely that many sarcomas of this histogenesis have never been so labeled because the anaplasia on the one hand or the preponderance of fibroblastic tissue on the other has kept the examiner from labeling the histogenesis as of striated-muscle origin

Opportunity to study the rhabdomyosarcoma has been afforded by Nettleship's discovery of a spontaneous, transplantable mature type rhabdomyosarcoma of Strain C mice The Nettleship tumor is histologically similar to such tumors in man and in domesticated animals but contains more adult-type cells with intact cross-striations and myofibrillae

A promising aid for the microscopic detection of rhabdomyosarcomas has been the study of tissue cultures made from the human tumor in which the muscle cells are more readily identified This important technic, developed by Margaret Murray and Arthur Purdy Stout, stems from earlier tissue culture studies performed by Irene Pogogeff

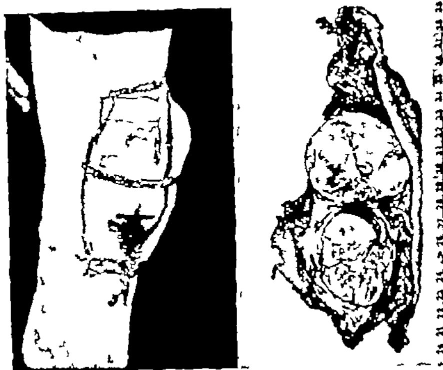


FIG. 350 (*Left*) Clinical appearance of a rhabdomyosarcoma involving the medial aspect of the left thigh in a 68-year-old male and which produced pulmonary metastases. The ports for preoperative palliative irradiation may be noted. (*Right*) Cross specimen of neoplasm resected for palliation. Note necrotic regions, which were yellow in the fresh specimen, and the multilobular appearance showing pseudoencapsulation (Pack and Eberhart, Surgery 32 1023 1952.)

and Margaret Murray in which skeletal muscle tissues of the adult rat were grown in vitro They were able to observe muscle fibers from the fourteenth to fifteenth day of the culture. On the sixteenth day they observed the fibers to contract spontaneously and on the eighteenth day of tissue culture, with the fibers still contracting, cross-striations were observed. The application of this method of diagnosis to the analysis and study of human tumors of questionable muscle origin is most promising.

Normal skeletal muscle of veretebrates exhibits a constant and characteristic histologic pattern. The cross striations of human skeletal muscle fibers are striking and are associated with less conspicuous, lighter and darker linear fibrils running at right angles along the length of the fiber A sarcomere is defined as the division of the fibril between two cross lines, and the fibrils are designated as sarcostyles It has been suggested that the beading of the sarcostyles is due to the distention of the sarcostyle during muscular contraction, which causes it to bulge out between the discs The nuclei of striated muscle are distributed irregularly along the fibers and immediately beneath the sarcolemma. The nuclei are about 10 microns in length and 5 microns in transverse diameter The capillary blood vessels in normal muscle are numerous but course in the interfibrillary spaces without entering the fibers The skeletal muscle is invested by a coarse sheath surrounding the entire muscle bundle, from which partitioning membranes are bundled into various sizes and ultimately form more delicate subdivisions between the individual muscles and fibers The connective tissue component of the rhabdomyosarcomas varies greatly in proportion to the amount of tumor present and possibly modifies the rate of growth and course of the disease.



Fig 351 Rhabdomyosarcoma of the thigh, illustrating the close relationship of the muscle sarcoma to bone A second tumor focus was found on the opposite side of the thigh Treatment consisted of hip-joint disarticulation Segmental resection of the lung was performed 4 years later for two metastatic foci (Pack and Eberhart, Surgery 32 1023, 1952)



Fig 352 Rhabdomyosarcoma of the forearm The dissected specimen illustrates a common relationship of the tumor to muscle groups and tendons (Pack and Eberhart, Surgery 32 1023, 1952)

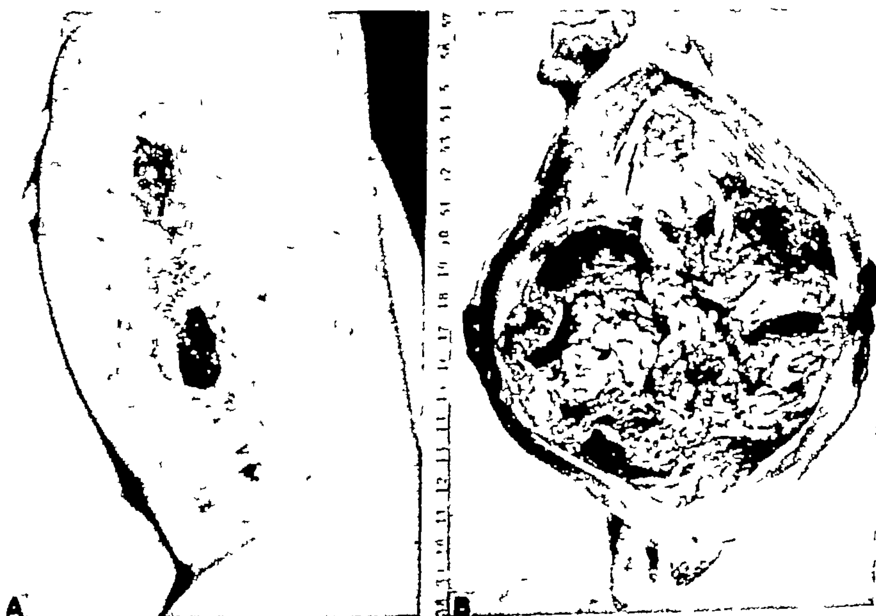


Fig 353 *A* Rhabdomyosarcoma of arm, recurrent and fungating through wound of previous attempted excision elsewhere Treated by interscapulothoracic amputation *B* Gross specimen of rhabdomyosarcoma in *A*, showing hemorrhagic necrosis and liquefaction in recurrent tumor, which is confined to the belly of the biceps brachialis (Pack and Eberhart, Surgery 32 1023, 1952)

The diagnostic and microscopic features of rhabdomyosarcoma have been summarized by Rakov as follows (1) a pronounced polymorphism of the tumor cells (2) the presence of spindle cells, (3) the presence of giant cells, (4) the peculiar arrangement of the stroma, and (5) the presence of fibrils which are sometimes cross striated

No one description of the microscopic picture of rhabdomyosarcoma can suffice, because *in certain instances the tumor* may duplicate in structure the spindle-cell sarcoma of smooth muscle and in other instances though within the same tumor exhibit a multinucleated myoblastic stage in which the cells are large, elongated, and multinucleated This is a feature of the rhabdomyosarcoma all phases of the histogenesis of the tumor are shown from areas of small spindle cells evidently representing the mesenchymal condensation from which the early muscle tissue originates, to the more differentiated portion of the tumor which may exhibit both the cross and longitudinal striations As far as possible the term *rhabdomyosarcoma* is used to denote those tumors arising in *striated muscle* and which are made up

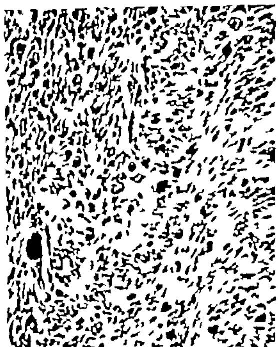


Fig. 354. Rhabdomyosarcoma of skeletal muscle The neoplastic cells are distributed in fasciculate fashion. (Pack and Eberhart, Surgery 32 1023 1952.)

of cells possessing the characteristi that are generally accepted of rhabd myoblasts

Tumors of myoblastic origin may b identified in the absence of definite cross-striated cells by the presence c centriole clusters and abortive fibril fo mation according to Wolbach. Arthu Purdy Stout has done much to clarif

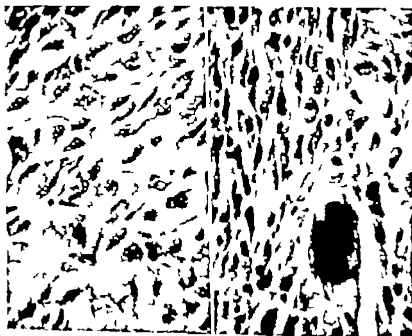


Fig. 355. Rhabdomyosarcoma of skeletal muscle exhibiting giant, racquet, and ribbon cells characteristic of the tumor (Pack and Eberhart Surgery 32.1023, 1952.)



FIG 356 Rhabdomyosarcoma Plasmodiallike syncytium cells in mitosis (Pack and Eberhart, Surgery *32* 1023, 1952)

our knowledge about the histogenesis of this tumor, and we therefore present his classification of the cell types The rhabdomyoblastic tumor cell appears in three forms, in each of which the cytoplasm is eosinophilic and often granular (1) the rounded-cell type, (2) the strap-shaped cell with two or more nuclei arranged in tandem formation, and (3) the racquet-shaped cell with a single nucleus at one expanded and rounded end and with a tapering body Using either Heidenhain's hematoxylin or Masson's trichrome stain containing acid fuchsin or phosphotungstic acid-hematoxylin with Zenker's fixation, Stout has usually been able to distinguish either the cross-striations or the longitudinal myofibrils in the cells of these tumors

The predominant cells of the rhabdomyosarcoma are long, spindle-shaped, relatively large (up to 100 microns) cells with homogeneous or granular acidophilic cytoplasm The nucleus is situated either in the center of the cell or unipolar, under which circumstances the cell tends to assume a racquet shape

The nuclei have been described as bean-shaped by Rakov, and the tandem arrangement of these bean-shaped nuclei produces the strap-shaped cell described by Stout The cells may bifurcate at the end and form syncytial arrangements with many nuclei Rakov believes that fibrils are most frequently seen in these syncytial masses. Vacuolization is occasionally seen in the peripheral cytoplasm Mitoses are not commonly seen in the microscopic field

Other types of cells are scattered among the spindle-cell elements These include a small round cell with a dark compact nucleus and narrow rim of cytoplasm, and a large polygonal cell with a pale vesicular nucleus In all the rhabdomyosarcomas studied by Rakov at the Oncological Institute in Leningrad, he found giant cells of some type, and he regards their presence as an indispensable diagnostic feature of rhabdomyosarcoma He divides the type of giant cells occurring in rhabdomyosarcomas into three groups. (1) the ordinary tumor giant cell 30 to 60 microns in diameter with a single bean-shaped nucleus and finely granular cytoplasm, (2) large spindle-shaped cells measuring 150 to 200 microns in length, and (3) a plasmodiallike cell, which is a rare type of giant cell consisting of an enormous oval or round structure covering more than a single high-power microscopic field and containing ten or more nuclei of varying size and shape

One of the most important features of rhabdomyosarcoma from a diagnostic viewpoint, is the presence of fibrils, chiefly cross-striations Although they have been described as occurring in all the cell types, most histologists have agreed that they are predominant in the spindle-cell syncytial arrangement The transverse striations are perhaps most readily seen in the teratomas or mixed-cell tumors in which there are muscular elements as a part of the complex tumor mass, but the cross-striations are

truly seldom conspicuous in the cells of the rhabdomyosarcomas arising in skeletal muscles. Demonstration of these *striations* establishes the diagnosis of rhabdomyosarcoma with certainty but unfortunately there exist many instances in which the fibrils cannot be demonstrated. Their demonstration, even when present, often requires an extremely skillful staining preparation and meticulous *microscopic* study In 39 cases of rhabdomyosarcoma reported by Jönnson, he *did* not find *fibrils* in a single instance. In the absence of fibrils, the pathologist must depend on the cellular components and structural arrangement in order to make the diagnosis

For complete and detailed descriptions of the histologic character of the *rhabdomyosarcoma, one may read* the papers by Stout, Rakov and Wolbach.

RATE OF GROWTH

The clinical course of this tumor falls into one of three growth patterns as *originally noted by Gordon-Taylor* (1) The neoplasm may remain small and *quiescent for many months or even years* and then suddenly exhibit an exacerbation of growth which may be spontaneous or possibly induced by trauma. (2) The tumor may grow in a fulminating acute manner from its onset, metastasize early be recalcitrant to any form of treatment and cause death within a short time. (3) The rhabdomyosarcoma may grow *slowly for weeks or months* The hazard in this last instance lies in the *inducement to operate too conserva*tively so that an unnecessarily large number of recurrences develop

Harper and Feder record an unusual instance of a rhabdomyosarcoma occurring in the sternocleidomastoid muscle of a 75-year-old Negro whose tumor had existed for 50 years without growth and then rapidly enlarged the microscopic *diagnosis was made by James Ewing In* one of our patients, the tumor was known to have been present 11 *years* before treatment was instituted.

Some interest attends the duration of time between the appearance of the first symptom or sign of a mass and the *first visit to a physician.* The failure to see a physician is due in all probability to the characteristic lack of pain and to the equally characteristic failure of the tumor to produce dysfunction of the part. A third deterrent is undoubtedly the fear of an unpalatable surgical opinion. In the *present series* a statement of the known duration of the tumor before initial treatment was available in 85 patients (Table 70) A perusal of this table shows that the patients dying of rhabdomyosarcoma came four months earlier for treatment than those patients who were cured. This paradox is readily understandable because the more highly malignant sarcomas grow more rapidly and induce greater apprehension in the patients

METASTASES

It is surprising that metastases do not *consistently* occur if we consider the fact that the muscles contract forcibly and often on the enclosed sarcoma. It is not the large myoblasts with striated fibers that usually are disseminated but the more primitive anaplastic round and spindle cells which metastasize to distant sites where they differentiate *after* implantation (Cappell and Montgomery) *The mode of extension* plays some role in the diffusion of the sarcoma, particularly its local growth, where it spreads more readily along the fascial planes than it does along the intermuscular spaces.

The rhabdomyosarcomas have an abundant vascular supply *and* tend to metastasize early to the lungs which are by *far* the most frequent site for metastases In 39 out of 39 of our unsuccessful cases, there was positive x ray evidence of pulmonary metastases Gen

eralized metastases (bone, skin, brain, viscera) are rare, but the spinal column is sometimes secondarily involved

It is not generally known that sarcomas of striated muscle can and do metastasize through lymph vessels to regional lymph nodes, which in our series of 100 patients occurred 6 times (6 per cent) or in 15 4 per cent of our unsuccessful cases The metastases in lymph nodes are prone to undergo necrosis and hemorrhage, the tumor tissue within the nodes has an alveolar architecture which simulates anaplastic carcinoma and may be erroneously diagnosed as such

REGIONAL LOCATION

The approximate location of the rhabdomyosarcoma in each patient is shown in Figure 357 The percentage distributions in the various locations are tabulated in Table 69 The upper extremity, including the shoulder, was involved in 34 cases (34 per cent), and the lower extremity, including the buttock and groin, was the site of the tumor in 54 cases (54 per cent). The regional distribution of rhabdomyosarcoma does not follow the pattern of most other soft part sarcomas, inasmuch as there is a definite predilection for the lower extremity and particularly for the thigh muscles In this series the individual muscles most often affected were the quadriceps, the abductor muscles of the thigh, the biceps, and brachialis.

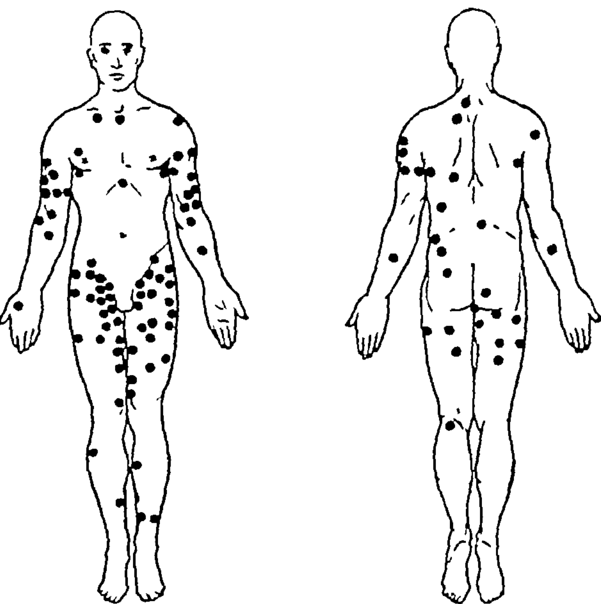


Fig 357 Scattergram illustrating regional distribution of rhabdomyosarcoma (Pack and Eberhart, Surgery 32 1023, 1952)

Gordon-Taylor found the rhabdomyosarcomas to have a predilection not only for certain segments of the extremities but even for certain muscles He quotes Durante who stressed the special vulnerability of the rectus femoris, the triceps of the arm, the muscles of the lower leg, especially the deltoid muscle, and the glutei muscles. Rakov of Leningrad found six rhabdomyosarcomas occurring in the thigh, three in the arm, four in the shoulder girdle, one within the thorax, and one in the lumbar region. One fact of uncertain significance which has appeared as a result of analysis in the present series is that the curability of rhabdomyosarcomas of the arm (45 5 per cent) is twice as great as for rhabdomyosarcomas of any other regional location

TABLE 69 RHABDOMYOSARCOMA OF SKELETAL MUSCLES LOCATION OF TUMOR

Regional Site	*Number*	*Percent*
Total cases	100	100
Hand	1	1
Arm	27	27
Shoulder	6	6
Leg	9	9
Thigh	41	41
Buttock	3	3
Groin	4	4
Chest, back, and abdominal wall	9	9

Geschickter has commented properly on the extremely rare occurrence of rhabdomyosarcomas in the spinal muscles of the body wall which were derived from the paraxial mesoderm This rarity of tumor formation, he thought,

was probably dependent on the ex tremely early differentiation of these structures T M Peery and W A. Smith reported the second case of pri mary rhabdomyosarcoma of the dia phragm this occurred in a 14-year-old Negro boy on whom a necropsy was obtained.

Palumbo Leibovitz, and Corcoran collected 208 cases of rhabdomyosarcoma from medical literature and reported the distribution of these tumors as fol lows skeletal muscles, 121 epididymis, 1 uterus 22, spermatic cord, 1 prostate, 18 urinary bladder 9 orbit 19 and testis 17

Arthur Purdy Stout has made the statement that, although the striated muscle tumors may occur most common ly within the skeletal muscle groups of the body yet they may also be found sporadically in the genitourinary system —urinary bladder kidneys prostate, testis, spermatic cord, uterus, vagina, round ligament, ovary—and in the heart, upper respiratory tract, gastrointestinal tract, and orbit.

RHABDOMYOSARCOMAS OF THE HEAD AND NECK IN CHILDREN

Stobbe and Dargeon have reported 15 cases of embryonal rhabdomyosar coma of the head and neck in children and adolescents from the records of the Memorial Hospital These cases are not included in the series presented here nor are they represented in the statistical analysis These 15 children aver aged 6 years of age with the youngest only 16 months old and the oldest 16 years. An equal incidence between the sexes was found, and there was no apparent familial predisposition The loca tion of the tumor was the orbit and region of the internal canthus, 4 cases the tonsil and the soft palate, 4 cases the mastoid and internal ear 2 cases with the remaining 5 neoplasms distributed in the regions of the neck, temple, zygoma, and parotid. The mean time in terval between the onset of symptoms to the time of treatment was three and one-half months The initial complaints depended on the location of the primary tumor and, in addition to the presence of the neoplasm, were listed as dys phagia, abnormal phonation, cough, di vergence of the eye, deviation of the jaw and discharge from the ear Six postmorten examinations were available for review metastases were discovered in cervical and mediastinal lymph nodes lungs, pleura, ovaries, peritoneum, ver tebral column femurs kidneys uterus, pancreas, thyroid, and brain Stobbe and Dargeon found recurrences to occur frequently after excision, x ray or radium therapy the recurrences often in multi ple foci, appeared in two weeks to one year—usually within three months after the previous treatment. Two of the 15 children were living without recurrences for more than eleven years their treat ment had been radical aggressive sur gery supplemented by x ray and radium therapy

SIGNS AND SYMPTOMS DIAGNOSIS

On theoretical grounds, the tumors of skeletal muscle would seem so readily accessible that early diagnosis and defin itive treatment would be the rule The contrary pattern of action apparently is due to the fact that the tumor is usually of silent growth. Pain is an infrequent complaint and occurred in only 17 pa tients in this series, of whom only one experienced discomfort in severe de gree. Usually the ache or discomfort resulting from a deep-seated muscle tumor is dismissed as a "stretched muscle" or a "charley horse," with corre sponding treatment, i.e massage, dia thermy etc. Gordon Taylor has com mented on the significant frequency of the insidious onset and development of these tumors. He has observed that they betray their appearance many times in



FIG 358 Rhabdomyosarcoma of inner aspect of the thigh, the most common location of this tumor (Pack and Eberhart, Surgery 32 1023, 1952)



FIG 359 Fungating recurrent rhabdomyosarcoma of the medial aspect of the left upper thigh (Pack and Eberhart, Surgery 32 1023, 1952)

the form of a painless, localized swelling, the absence of pain, the mental hebetude of the average patient regarding a lump which does not interfere with normal activities, or the fear of an unpalatable surgical opinion tending to keep the operator and victim apart until

TABLE 70 RHABDOMYOSARCOMA OF SKELETAL MUSCLES DURATION OF SYMPTOMS PRIOR TO INITIAL TREATMENT IN RELATION TO END RESULTS

Type of Case	*Average in Months*
Total cases	6 6*
Patients living and well	8 7
Patients who died of rhabdomyosarcoma	4 7
Patients dead of other causes or lost to follow-up	7 7
Recent group	6 9

* Excludes one patient with a history of 11 years

the tumor has often attained a considerable size Interference with function of the affected extremity is a late manifestation and may be in marked contrast to the size of the tumor Limitation of motion may occur only when the tumors are located in close proximity to a joint, and the onset of early pain is more apt to occur whenever the neoplasms are situated adjacent to a nerve trunk

There is considerable variation in the clinical appearance of the tumor The neoplasm may be located superficially and appear to be discrete, encapsulated, and freely movable On the other hand, there may be a deep-seated, fusiform mass producing distortion of the involved muscle or muscle groups If the involved muscle can be made to relax, the tumor will usually be movable in all directions This mobility characteristically disappears when the muscle is contracted Changes in mobility with relaxation or contraction of the muscle is an important feature and points to a muscular localization of the tumor The skin and subcutaneous tissues immediately overlying the tumor are usually unchanged There may be a fine network of dilated veins In a few instances the tumor infiltrates the skin and gradually produces pressure necrosis, ulti-

mately leading to a mushroomlike, ulcerated, bleeding cutaneous mass

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis of rhabdomyosarcoma involving skeletal muscles, there are a number of different lesions which simulate this neoplasm. Among them, of course are the numerous varieties of malignant and benign tumors of the soft somatic tissues of varied histogenesis Even a deeply situated lipoma may be confused with rhabdomyosarcoma because of its firmness on contraction of the surrounding muscle groups Aspiration biopsy and the demonstration of the translucence of the deep lipoma on roentgenography are practical distinguishing features Intramuscular cysts and unresolved deep hematomas are sometimes extremely difficult to distinguish from rhabdomyosarcoma, because the latter lesion occasionally undergoes intratumoral hemorrhage with infarction and necrosis Muscle angiomas have always been diagnostically confused with this tumor except for the fact that they commonly cause more discomfort, usually show calcium depositions in the substance of the neoplasm, and increase in volume on motion of the affected part.

Tumors of the skeletal muscles would seem to be so accessible that early diagnosis and treatment would be the rule, but unfortunately their deep location and the usual absence of pain and disability conspire to delay the diagnosis until the lesion has often reached bulky dimensions This asymptomatic and nondisabling presenting mass, usually deeply situated is the common way in which the tumor heralds its appearance. The deeply situated rhabdomyosarcomas may give the false impression of immobility but they are seldom fixed the probable explanation lies in the origin or insertion along the bone of the involved muscle groups The mobility of the tumor when the muscle is relaxed and the immobility when the muscle is contracted have been accepted by numerous authors There is very little mechanical interference with muscular function until the tumor perforates the sheath of the muscle and by invasion becomes attached to adjacent fixed structures As a rule skin and superficial tissues move over the tumor and the tumor moves over the underlying bone. In commenting on the fact that the rhabdomyosarcoma changes in position with contraction (shortening) and relaxation (elongation) of muscle, Bick has stated a law which is pertinent and acceptable "The amplitude of change in position during muscle activity diminishes as the situation approaches the functional mid point of the muscle, and increases as it is distant from that point."

TREATMENT OF RHABDOMYOSARCOMA

Radiosensitivity and Radiation Therapy

Radiation therapy alone is not sufficient to destroy the average rhabdomyosarcoma such treatment is often followed by necrosis and hemorrhage into the body of the tumor and later reactivation and diffuse invasive growth. Rhabdomyosarcomas are relatively radioresistant. Postoperative irradiation by the fractionated dose principle has been advocated and employed as an adjunct to radical local dissection on the principle of inducing sufficient additional interstitial fibrosis throughout the operative site as to inhibit or delay any tendency to recurrence. There have been some instances in our experience in which preoperative irradiation has converted a technically inoperable sarcoma to one which was successfully removed two of these patients are living and well more than 10 years since the dates of operation It is superfluous and procrastinating to administer preoperative irradia

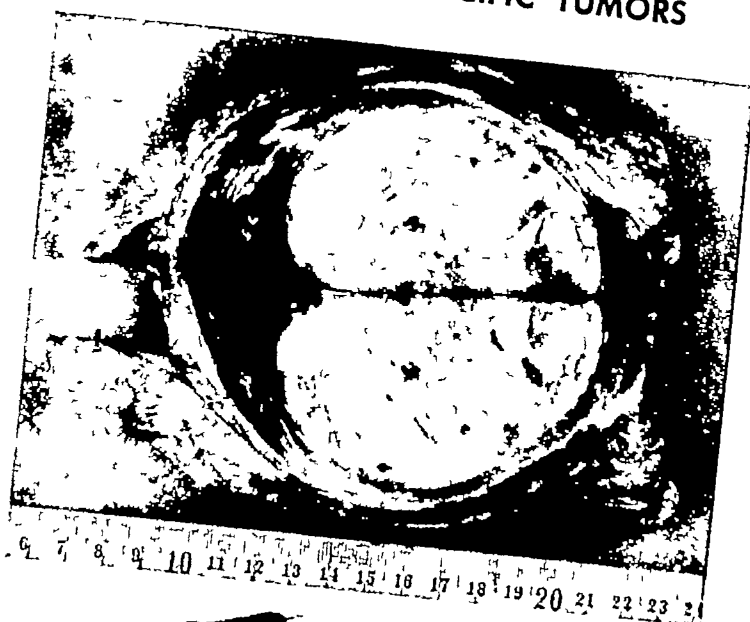




FIG 360 Gross specimens of rhabdomyosarcomas from two different locations (*Upper*) Rhabdomyosarcoma of the arm (*Lower*) Rhabdomyosarcoma of the buttock

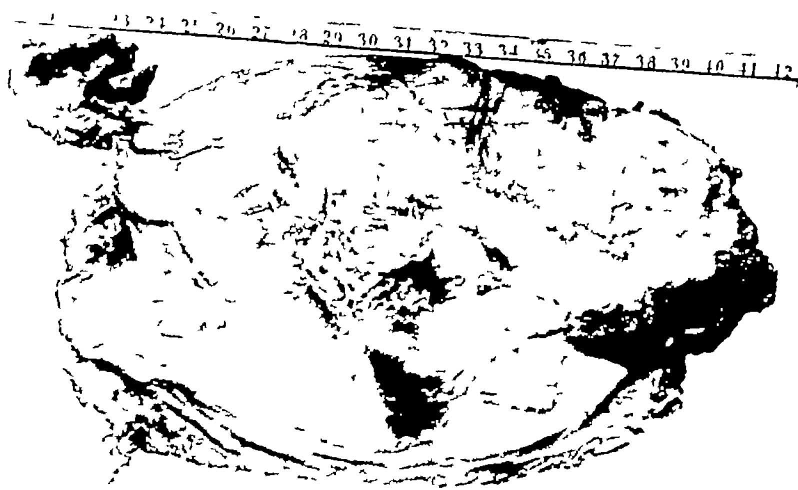


FIG 361 Gross specimen of rhabdomyosarcoma of the thigh Treated by wide local excision and postoperative irradiation Patient succumbed from pulmonary metastases 1½ years after treatment No local recurrence (Pack and Eberhart Surgery 32 1023, 1952)

tion if the surgeon contemplates an amputation of the extremity Therefore, we may say that radiation therapy should never delay surgical treatment if the sarcoma is operable radiation therapy should never be substituted for surgical treatment so long as a cure remains possible.

Irradiation, either alone or preoperatively or postoperatively was used in 61 cases It is difficult to assess the value of irradiation, because it was used so frequently in combination with excision or amputation. There were 11 patients who received preoperative irradiation in the form of x rays or radium-element pack, in 9 of these there was definite local recurrence of tumor or the surgically excised specimen showed viable tumor cells Forty four patients received



Fig 362. Lateral and anteroposterior laminagrams demonstrating the presence of a solitary metastasis from a rhabdomyosarcoma of the thigh which had been treated previously by radical amputation.



Fig. 363. The gross specimen of the metastatic rhabdomyosarcoma shown in the laminagrams in Fig. 362, procured by lobectomy

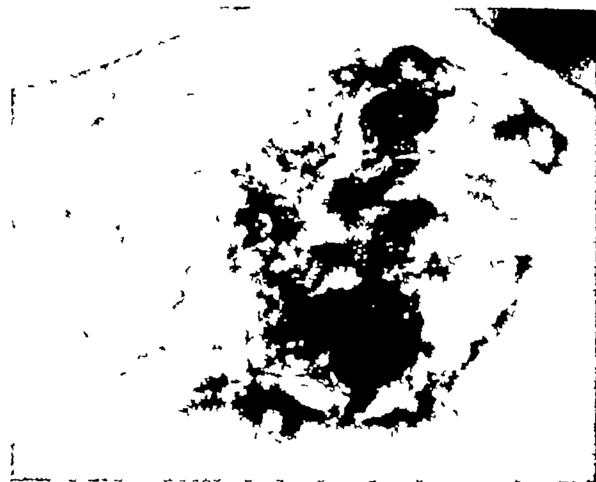


FIG 364 Multiple recurrences following wide and deep excision of a rhabdomyosarcoma of the interscapular region, a characteristic feature in the natural history of this disease (Pack and Eberhart, Surgery 32 1023, 1952)

some type of postoperative irradiation, 25 of them developed definite local recurrence following completion of the irradiation On the basis of these data, we can say that these tumors are not radiosensitive, and irradiation cannot be depended upon to prevent local recurrence when it is given following an inadequate local excision.

SURGICAL TREATMENT

Treatment in these patients has consisted of surgical excision, irradiation (preoperatively and postoperatively), radium in the form of radium-element pack or radium needles, and amputation These therapeutic methods have been used singly and in various combinations A glance at our tabulation shows that very few patients were treated exclusively by one form of therapy Surgical excision as the initial method was done in a total of 58 cases (all groups included) In 7 patients it was the only treatment The remaining patients had additional therapy in the form of postoperative irradiation, amputation, or a combination of both

The indications for and technic of wide local excision are discussed at length in Chapter 8

The choice between radical surgical dissection and amputation depends on innumerable factors such as the degree of malignancy, the regional location, fixity or mobility, the primary or recur-

TABLE 71 RHABDOMYOSARCOMA OF SKELETAL MUSCLES OPERABILITY ACCORDING TO YEAR OF ADMISSION

	Total Cases		*1928–1933*		*1934–1938*		*1939–1943*		*1944–1948*	
Type of Case	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent.*
Total cases	100	100 0	3	100 0	30	100 0	44	100 0	23	100 0
Cases receiving definitive treatment	75	75 0	2	66 7	22	73 3	32	72 7	19	82 6
Primary operable cases	24	24 0	0	0 0	7	23 3	9	20 4	8	31 8
Recurrent operable cases	45	45 0	0	0 0	11	36 7	23	52 3	11	47 8
Cases receiving postoperative prophylactic x-ray therapy (surgery performed elsewhere)	6	6 0	2	66 7	4	13 3	0	0 0	0	0 0
Cases receiving palliative treatment or none	25	25 0	1	33 3	8	26 6	12	27 3	4	17 4
Primary inoperable cases	7	7 0	0	0 0	4	13 3	2	4 5	1	4 3
Recurrent inoperable cases	7	7 0	1	33 3	1	3 3	4	9 1	1	4 3
Cases refusing treatment	11	11 0	0	0 0	3	10 0	6	13 6	2	8 7

Table 72 Rhabdomyosarcoma of Skeletal Muscles Location of Tumor in Relation to Five year Survival without Sarcoma

Location of Tumor	Cases Through 1943			5-year Survivals		Distribution of Determinate Cases						
						Primary Operable		Recurrent Operable		Prophylactic Irradiation		Inoperable
	All Cases	Indeterminate Cases	Determinate Cases	Number	Percent (Based on Determinate Cases)	Number	5 year Cures	Number	5-year Cures	Number	5 year Cures	Number
Total cases	77	12	65	22	33 8	10	4	31	14	6	4	12
Arm	22	4	18	10	55 6	3	1	12	8	1	1	1
Shoulder	5	1	4	2	50 0	0	0	4	2	0	0	1
Leg	6	1	5	2	40 0	2	0	2	1	1	1	0
Thigh	30	5	31	5	10 1	7	1	11	2	4	2	9
Buttock	2	0	2	1	50 0	1	1	1	0	0	0	0
Groin	2	1	1	1	100 0	1	1	0	0	0	0	0
Chest back abdominal wall	4	0	4	1	25 0	2	0	1	1	0	0	1

TABLE 73 RHABDOMYOSARCOMA OF SKELETAL MUSCLES AGE OF PATIENT IN RELATION TO FIVE-YEAR SURVIVAL WITHOUT SARCOMA

Age	Cases Through 1943			5-year Survivals		Distribution of Determinate Cases						
						Primary Operable		Recurrent Operable		Prophylactic-inoperable Irradiation		
	All Cases	Indeterminate Cases	Determinate Cases	Number	Percent (Based on Determinate Cases)	Number	5-year Cures	Number	5-year Cures	Number	5-year Cures	Number
Total cases	77	12	65	22	33.8	16	4	31	14	6	4	12
10 years and less	3	1	2	1	50.0	0	0	0	0	1	1	1
11–20 years	2	0	2	2	100.0	0	0	1	1	1	1	0
21–30 years	5	0	5	3	60.0	2	1	2	1	1	1	0
31–40 years	6	1	5	4	80.0	1	1	3	3	0	0	1
41–50 years	18	4	14	2	14.3	2	0	8	2	0	0	4
51–60 years	22	2	20	7	35.0	5	1	10	5	2	1	3
61–70 years	13	3	10	3	30.0	3	1	5	2	1	0	1
71 years and over	8	1	7	0	0.0	3	0	2	0	0	0	2

rent status, the presence of regional and distant metastases and most important perhaps the experience and judgment of the operator

Before a course of action is decided *the histologic diagnosis* should be established. If the sarcoma is recurrent, the original specimen is available for detailed study and special staining If the neoplasm has not been previously treated and *the clinical features* or aspiration biopsy have not been revealing, a formal incisional biopsy is done under tourniquet control and with frozen section analysis The immediate diagnosis is followed at once by positive action either surgical dissection or amputation

END RESULTS OF TREATMENT

Previous reports and opinions concerning the prognosis of rhabdomyosarcoma have been universally pessimistic. Palumbo Leibovitz, and Corcoran declared there were no known instances of cure of this tumor Arthur Purdy Stout, in reviewing 121 collected cases of which 108 underwent treatment, found only 4 patients who survived the five-year period of definitive cure· of these 4 patients 1 was treated by amputation 1 by excision alone, and 2 by excision and radiation therapy In contrast to these bad results we have 22 of 65 determinate cases whose treatment was conducted by us after a definite pattern, who are now living and well for more than five years from the date of primary treatment without recurrence during the elapsing interval Five of these 22 patients survived for more than ten years. This cure rate of 33 8 per cent is the highest yet reported in medical literature Twelve of these patients had involvement of the upper extremity in 8 the tumors were situated on the lower extremity and in 2 on the trunk. The curability of rhabdomyosarcomas in the arm was three times as great as that of tumors located in the thigh. An explanation of this disparity lies in the early recognition and more prompt acceptance of surgery for tumors of the upper extremity

Contrary to the generally accepted opinion, the prognosis for rhabdomyosarcoma is better in childhood and early life than it has been in patients in middle and later life.

The good end results deserve special attention in view of the distribution of these 65 determinate cases in the groups of primary operable, recurrent operable, and inoperable stages of the sarcomas at the time of application for treatment. Twelve of these patients had definitely inoperable sarcomas at the time they applied to us 10 of these received ir radiation only and 2 received no therapy other than symptomatic relief Only 18 of the 65 cases were classified as primary operable, and 31 patients, or almost half of them, applied to us for treatment with locally recurrent rhabdomyosarcomas still in an operable stage Fourteen of these patients had experienced three or more local recurrences which were treated by surgical excision, and 2 patients in this group had five local recurrences treated by dissection. In reviewing the cause of recurrence in this large group of recurrent, operable sarcomas which came to us after previous local excision elsewhere, it is apparent that the previous surgical dissection was conservative, consisting commonly of enucleation with no adherence to the rules for radical surgical dissection as given in detail in another section. A review of Table 74 would indicate that if recurrence develops following a local conservative procedure, the patient does not necessarily lose his life, because our records show that 14 of these 31 patients (45.2 per cent) with recurrent operable rhabdomyosarcomas are living and well five years after they applied to us for treatment. This five-year survival rate is higher than was obtained in the group

TABLE 74 RHABDOMYOSARCOMA OF SKELETAL MUSCLES TYPE OF TREATMENT IN RELATION TO FIVE-YEAR SURVIVAL WITHOUT SARCOMA

(Based on determinate cases)

	Total Cases			*Primary Operable*			*Recurrent Operable*			*Inoperable Cases*
		5-year Cures			*5-year Cures*			*5-year Cures*		
Type of Treatment	*Total Cases*	*Number*	*Percent*	*Total Cases*	*Number*	*Percent*	*Total Cases*	*Number*	*Percent*	*Number*
Total cases	65	22	33 8	16	4	25 0	31	14	45 2	12
Excision only	7	4	57 1	3	2	66 7	4	2	50 0	0
Excision and irradiation	21	7	33 3	8	1	12 5	13	6	46 2	0
Amputation	6	3	50 0	2	0	0 0	4	3	75 0	0
Dissection	6	3	50 0	2	1	50 0	4	2	50 0	0
Interscapulothoracic amputation	5	1	20 0	1	0	0 0	4	1	25 0	0
Hip-joint disarticulation	2	0	0 0	0	0	0 0	2	0	0 0	0
Postoperative prophylactic irradiation	6	4	66 7	0	0	0 0	0	0	0 0	0
Irradiation only	10	0	0 0	0	0	0 0	0	0	0 0	10
No treatment given	2	0	0 0	0	0	0 0	0	0	0 0	2

TABLE 75 RHABDOMYOSARCOMA OF SKELETAL MUSCLES FIVE-YEAR END RESULTS

Total cases				100
Indeterminate cases				35
(Patients refusing treatment, not completing treatment, lost track of, or treated elsewhere)				
Determinate cases, for evaluating five-year cures			65	
Failures died with sarcoma			41	
Living without sarcoma under five years after treatment for recurrence			2	
Successful results without sarcoma five years or more			22	
5 to 10 years 17	Primary operable cases	4		
10 to 15 years 5	Recurrent operable cases	14		
	Prophylactic x-ray therapy	4		
Five-year-cure rate				
Successful results divided by determinate cases		22 65		33 8 per cent

of patients with primary operable rhabdomyosarcomas in which we had the first opportunity for treatment The paradox of securing a higher cure rate for recurrent operable sarcomas than for primary operable sarcomas in our experience is explained by the fact that those patients whom we saw without previous surgical treatment had more advanced tumors in such a location and of such extent as to discourage surgeons from attempting a simple enucleation

TUMORS OF STRIATED SKELETAL MUSCLE (BENIGN AND MALIGNANT) CASE REPORTS*

CASE REPORT NO 62: BENIGN EMBRYONAL MYOBLASTOMA OF TONGUE

C. T., a 12 year-old girl had been aware of a swelling at the base of her tongue for six months prior to the date of admission to the hospital. Four days before admission she expectorated blood which was followed later by hematemesis of a large quantity of blood. Bleeding occurred intermittently for four days and was extremely difficult to control.

On admission, a large tumor 5 × 6 × 4 cm. was found occupying the base of the tongue posterior to the circumvallate papillae. It extended far down into the hypopharynx and partially occluded the oropharynx. A bilateral ligation of the external carotid arteries was performed. The tumor at the base of the tongue was enucleated without difficulty A temporary tracheostomy was performed. The defect in the tongue was closed by interrupted catgut sutures The pathologic report was embryonal myoblastoma of the tongue, benign (Abrikossoff's tumor) There has been no recurrence in the succeeding six years. (Fig 344)

CASE REPORT 63: CONGENITAL RHABDOMYOSARCOMA OF THIGH (17 YEAR CURE)

G McG., a male infant, had on the anterolateral aspect of the left thigh a small lump which developed shortly after birth and grew slowly At two months of age, his mother became sufficiently apprehensive to seek medical consultation A radical surgical excision of the mass with the surrounding fascia and muscle was performed. The tumor was a sarcoma Grade III, with some foci strongly suggesting rhabdomyosarcoma.

A bivalved body cast was applied with a fenestrated opening overlying the thigh in order to immobilize the infant while x ray treatment was administered. High voltage x ray therapy was given using the following factors 200 000 volts 50 cm target–skin distance, 0.5 mm. copper filter 9 × 8 cm field, 25 ma 150 r daily for a total dose of 2400 r 2280 r delivered to the center of femur

The child is now living and well without shortening of the extremity without crippling deformity and without recurrence. He is 16 years of age. (Fig 7)

CASE REPORT NO 64: RHABDOMYOSARCOMA OF PROSTATE

G E a 47 year-old male had symptoms of prostatic enlargement with partial urinary obstruction in January 1940 A two-stage suprapubic prostatectomy was performed. The prostate contained a soft tissue tumor pronounced by Dr Fred W Stewart to be a rhabdomyosarcoma. Fourteen months after the date of operation, he complained of urinary frequency and a sensation of pressure within the rectum.

On physical examination he was found to be a vigorous male in apparently good health On rectal examination a bulky lobulated, semifixed tumor was palpated in the region of the prostate where it projected into the rectal ampulla and invaded the rectal wall A roentgenogram of the chest revealed no evidence of pulmonary metastasis

The choice of treatments at that time was to do either a total cystectomy and abdominoperineal rectal resection with ureteral implantations or to rely on combined external and interstitial irradiation

Employing the million volt x ray apparatus with 2 mm of mercury and 8 mm of copper filter 70 cm. target–skin distance 3 ma of current, with treatment to 3 ports, namely left pelvis posteriorly right pelvis posteriorly and direct suprapubic fields giving 300 r daily and alternating, a total dose of 3000 r × 3 was administered, supplemented by a perineal port with fractions of 300 r for a total dose of 2100 r Under

* The following case reports, by Pack and Eberhart, appeared in Surgery 32:1023, 1952, and are included here by permission of the authors and the publisher C. V Mosby Company



FIG 365 Benign myoma of gubernaculum testis (*Courtesy*, Dr Gordon McNeer Case report No 65) (Pack and Eberhart, Surgery 32 1023, 1952)

spinal anesthesia and with finger guidance in the rectum, the bulky tumor was implanted with 53 mc of radon in gold seeds through the perineum Regression was immediate and apparently complete

The tumor completely regressed but as an end result of its solution, a rectovesical fistula developed which required a colostomy and a retention catheter This patient gained in weight and was in very good health until July, 1944, when he was treated for arterial hypertension, arteriosclerosis, dilation of the aorta, and the anginal syndrome He died of heart disease in March, 1945, with no evidence of recurrence of the prostatic sarcoma and no evidence of pulmonary metastasis on the date of death The period of survival without recurrence was 4 years subsequent to his last radiation treatment

CASE REPORT NO 65 MYOMA OF GUBERNACULUM TESTIS

J R , a 59-year-old male, had been aware for two months of discomfort in the right lower abdomen He later observed a mass in this region which slowly increased in size On examination the right testis was missing and presumably was situated intraabdominally A huge mass was felt in the right iliac quadrant, and a presumptive diagnosis of retroperitoneal tumor was made At laparotomy, a sausage-shaped, encapsulated, retroperitoneal tumor was found in the right iliac quadrant, its only point of attachment was near the right inguinal ring It was dissected intact by Dr Gordon McNeer It measured 28 × 11 × 11 cm On section it consisted of a large cyst cavity filled with dark chocolate-colored fluid, projecting within the cyst were numerous lobular tumors, the largest measuring 5 × 5½ × 7 cm They were coarsely fasciculated On microscopic examination, no testicular tissue was discovered and no evidence of any teratoid tumor of an intraabdominal testis The tumor was comprised of an adult type of smooth muscle resembling a uterine myoma The tubelike structure along the side of the tumor was the spermatic cord The presumptive diagnosis was myoma of the spermatic cord or gubernaculum testis The tumor was classified as benign (Fig 365)

CASE REPORT NO 66 RETROPERITONEAL EMBRYONAL RHABDOMYOSARCOMA OF GUBERNACULUM TESTIS

E L , a 5-month-old baby, was admitted to the hospital with a huge tumor, situated in the lower abdomen and pelvis and extending up to the umbilicus and as far as the midline A barium enema and roentgenograms of the colon revealed situs inversus The large bowel was displaced medially by the tumor Intravenous pyelography demonstrated extrinsic pressure on the left ureter with resultant hydronephrosis and hydroureter A previous attempt at surgical excision in another institution had

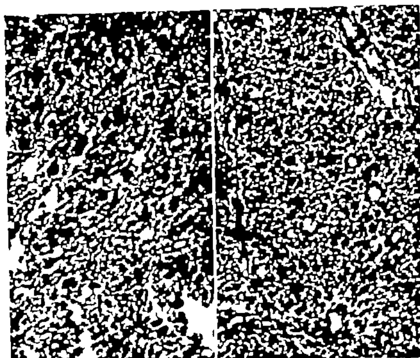


FIG. 366 Two sections showing the histologic variants of an embryonal rhabdomyosarcoma of the gubernaculum testis in a child. (Case report No. 66) (Pack and Eberhart, Surgery 32 1023, 1952.)

been unsuccessful Because of the proved radio-resistance of the tumor a second attempt at radical surgical dissection was done. The neoplasm was intimately adherent to the testis, but the testis was not a part of the true tumor The diagnosis was embryonal rhabdomyosarcoma, presumably originating from the gubernaculum testis. Within two months a recurrence developed deep in the pelvis and involved the urinary bladder fungating into the cavity causing obstruction of both ureters, and death from uremia. (Fig. 366)

CASE REPORT NO 67: RHABDOMYOSARCOMA OF VULVA METASTATIC TO GROINS

C. L., a 47 year-old woman was first seen on July 25 1949 Four years before (June 1945) a tiny deep spherical tumor was felt in the left vulva by the patient. It gradually grew in size until November 1945 when the labium minus was surgically excised with the contained tumor It was diagnosed as rhabdomyosarcoma. Nine post operative x-ray treatments were immediately given She was free of symptoms until November 1947 when she experienced discomfort in both groins. In March 1948 palpable inguinal masses were surgically dissected by another surgeon. An interval of freedom existed until March 1949 at which time severe pain occurred, particularly in the right groin. In June 1949 large masses



FIG. 367 Low-power photomicrograph of rhabdomyosarcoma of the vulva. Part of a complex tumor exhibiting some features of sarcoma botryoides. (Case report No. 67 See also Fig. 29)

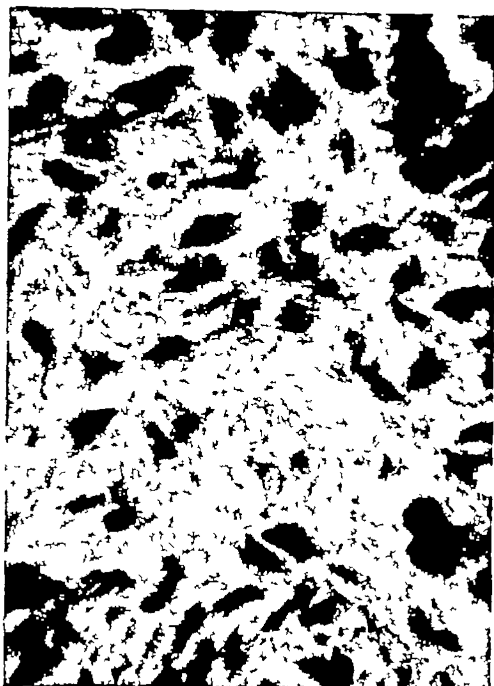


FIG 368 High-power photomicrograph of rhabdomyosarcoma of the vulva shown in Fig 367 (Pack and Eberhart, Surgery 32 1023, 1952)

were palpable in both groins The overlying skin showed the effect of chronic radiation dermatitis The masses involved the deep inguinal and femoral lymph nodes They were semifixed The diagnosis was recurrent rhabdomyosarcoma of the vulva with bilateral metastases to inguinal lymph nodes

Treatment

Radical vulvectomy with bilateral groin dissection The entire vulva was surgically excised, together with a wide segment of skin from both groins to include the underlying fat and fascia and all the lymph nodes in the femoral, inguinal, and deep iliac groups The inguinal ligaments were transected, and the dissections carried out retroperitoneally to the bifurcation of the aorta The operation was done by excision and dissection in continuity (Fig 29)

Pathologic Report

The site of the primary tumor contained no recurrent cancer The lymph nodes in the groin were involved by rhabdomyosarcoma The deep iliac nodes were free of evidence of metastasis

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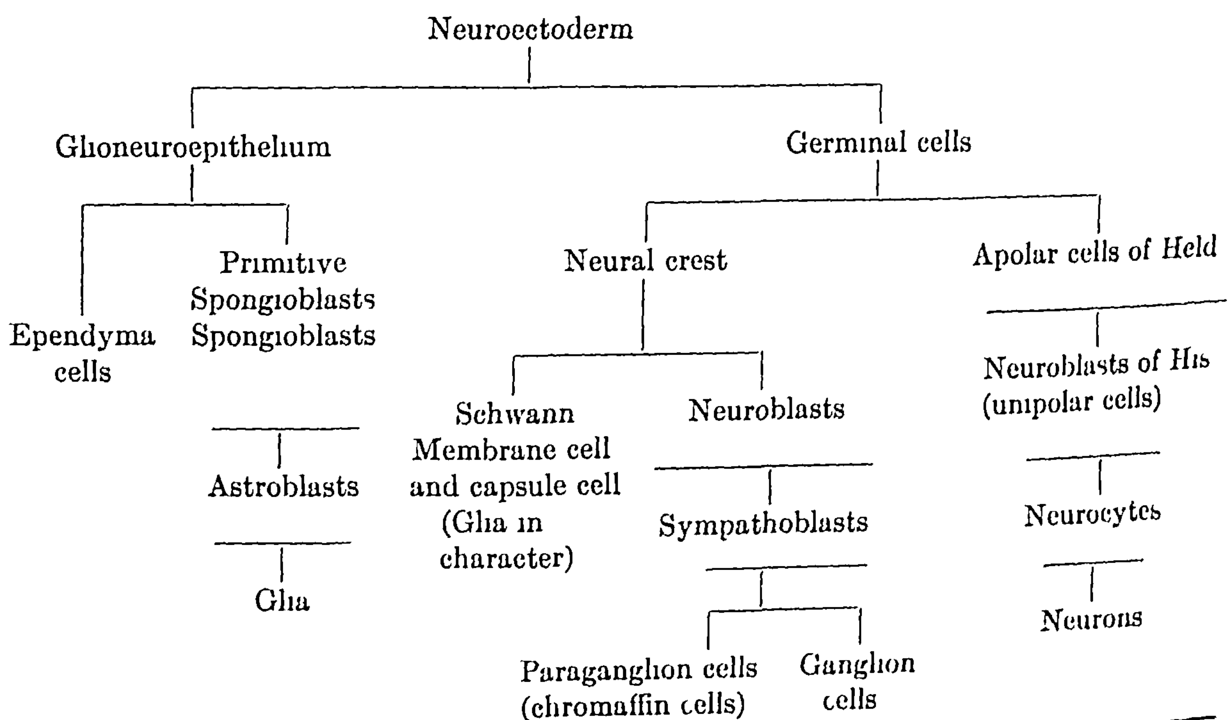
CHAPTER 23

Tumors of Peripheral Nerve Origin

INTRODUCTION

ANY presentation of sarcomas of the soft somatic tissues must discuss tumors of the peripheral nervous system All therapeutic attempts at their ablation embrace the surgical and radiologic principles for treating tumors of the torso and extremities It is understandable that tumors of the peripheral nervous system be clinically considered with mesodermal neoplasms because very early in embryologic development, the derivatives of the neural crest, the progenitors of the peripheral nervous system, infiltrate the mesoderm and become very closely aligned to the tissues of mesodermal origin Oncologically this neural infiltration is manifested by the compound nature of certain tumors of the neural and mesodermal systems, *e.g.*, nevi, neurofibromatoses, etc Tumors

TABLE 76 HISTOGENESIS OF NERVOUS SYSTEM*



* After Globus and Strauss

TABLE 77 TUMORS OF THE PERIPHERAL NERVOUS SYSTEM

Tissue of Origin	*Benign*	*Malignant*
1 Nerve	Amputation and traumatic neuromas Appendicial neuromas (not neoplastic)	Neurogenic sarcoma ?
2. Tissue covering nerves —cells of Schwann —(neurilemma)	Encapsulated neurilemmoma Plexiform (diffuse) neurilemmoma	Malignant neurilemmoma (Schwannoma)
3 Nerve and neurilemma	Neurofibroma (multiple neurofibromatoses)	?
4 End organs of nerves	Glomus tumor Cutaneous leiomyoma Pigmented mole	Malignant melanoma
5 Mesodermal tumors involving nerves	Hemangioma Lipoma ? Fibroma ?	Hemangiosarcoma Fibrosarcoma ? Neurogenic sarcoma ?
6 Tumor invading nerves		Direct invasion of neural sheath by intraneural metastases
7 Sympathetic ganglia	Ganglioneuroma	Sympathicoblastoma (neuroblastoma)
8 Paraganglionic cells (sympathetic and parasympathetic systems)	*Hormonally active pheochromocytoma* Adrenal medulla Retroperitoneal Posterior mediastinum (occasionally) *Hormonally inactive. paraganglioma* a Adrenal medulla b Mediastinal and retroperitoneal ganglia c Carotid and aortic bodies d. Glomus jugularis e. Ganglion nodosum of vagus nerve f Ganglion in sheath of glossopharyngeal nerve (middle ear) g Ciliary ganglion h Argentaffin cells	Malignant pheochromocytoma
9 Aberrant central nervous system tissue	Astrocytoma (glioma) Ganglioglioma	Glioma Nasal neuroepithelioma

After Stout

which are composed exclusively of nervous tissue are in such anatomic juxtaposition with the supportive tissues of the body that they must be considered in a discussion of therapy of tumors of mesodermal structures Many of the neoplasms of the peripheral nervous system are ectodermal in origin and are not, therefore, truly sarcomas. However common usage has attributed the designation of sarcoma to this group of neoplasms

Tumors of nervous tissue develop in practically every anatomic region of the organism. They arise from the central nervous system (brain and spinal cord) and in the peripheral nervous system beginning at their points of emergence from the spinal cord (usually the most



FIG 369 Plantar digital nerves (*Right*) Neuromatous swellings associated with Morton's neuralgia (*Left*) Normal nerve for comparison. (Lapidus and Wilson)

frequent location) they course through the mesodermal structures to their sites of termination, frequently in the skin, where nevi, glomus tumors, and others occur They arise from nerves, nerve sheaths, ganglionic cells, and paraganglionic structures Table 76 presents the histogenesis of the nervous system (after Globus and Strauss) and indicates the relationship of the cellular constituents of this system Table 77 is a classification of tumors of the peripheral nervous system

In the subsequent discussion tumors arising from the peripheral nervous system (parasympathetic and sympathetic nervous system) within the soft somatic tissues (torso and extremities) will be presented Those arising in other locations which have a bearing on the somatic tissues by nature of their anatomy will be described Thus, tumors of the posterior mediastinum frequently infiltrate the posterior parietes, and the surgical problems encompass those of the soft somatic tissues Those tumors of the peripheral nervous system which do not have a therapeutic bearing on the soft somatic tissues will not be dealt with here Thus, acoustic neuromas present problems of brain surgery, and argentaffin tumors of the appendix and intestine are primarily gastrointestinal surgical conditions

CLASSIFICATION

AMPUTATION AND TRAUMATIC NEUROMAS

Pure overgrowth of nerve elements is noted at times after amputation and is called *amputation neuroma* (in the appendix, *appendiceal neuroma*) The growth is orderly and not neoplastic In 1876 Thomas G Morton described the painful affection of the foot characterized by very sudden attacks of burning and cramp-like pain localized around the fourth metatarsophalangeal joint, usually precipitated by walking with shoes on and relieved by removal of the shoe and rubbing or manipulating the fourth toe During the attack the patient is unable to bear any weight on the affected foot Morton said that because of the absence of inflammatory symptoms and the neuralgialike character of the affliction, the severity of the paroxysms could be explained by either a neuroma or an hypertrophy of the nerve because the pain simulated severe facial neuralgia Morton thought that the plantar nerves were pinched between the metatarsal bones, and he resected this joint This theory has been discredited It is now known that Morton's neuralgia is an entity characterized by the formation of neuromas in the third common plantar digital nerve between the third and fourth metatarsal heads at or proximal to its division into separate branches to the adjacent surfaces of the third and fourth toes In

severe cases neurectomy is recommended to give relief

GLOMUS TUMOR AND CUTANEOUS LEIOMYOMA

The end organs of the peripheral nerves produce such tumors as the glomus tumor and the recently described *cutaneous leiomyoma (Stout)* (See pp 431 and 535)

TUMORS OF MESODERMAL ORIGIN IN PERIPHERAL NERVES

A group of benign and malignant tumors of mesodermal origin arise from mesodermal components of the peripheral nerves (hemangioma, hemangiosarcoma, and others) *Their treatment* is similar to that of tumors of mesodermal origin and is discussed in Chapter 19

NEVI AND MELANOMA

Masson and others attribute a neuroectodermal origin to melanoblasts and tumors of these cells (pigmented moles and malignant melanoma) are listed *in this classification of tumors of the* peripheral nervous system but their treatment will be presented in another *monograph because the therapy of this* group of neoplasms embraces specific therapeutic problems and the therapeutic principles of dermatologic neoplasms

METASTATIC TUMORS IN PERIPHERAL NERVES

Neural sheaths and the nerves themselves present a route for the transport of tumors from other primary locations Their presence is usually an ominous sign There is usually *no point of exit*, and they may thus traverse great distances to lodge in the central nervous system. *As more is learned about the* incidence and nature of this mode of spread, surgical technics may be developed for the extirpation of tumors and their metastases which travel by this route, similar to cancer operations developed on the basis of the lymphatic *spread of cancer*

Metastasis within perineural sheaths occurs in cancer of the oral cavity esophagus breast, rectum, prostate, lung, penis vulva pancreas and other organs Its occurrence may contribute to severe pain (rectum, prostate) or to symptoms *of obstructive jaundice in cancer of the* pancreas (Ariel and Shahon)

Nerves themselves are not infrequently infiltrated by cancer Parotid carcinomas may infiltrate the facial nerve bronchogenic carcinoma, the phrenic nerve, esophageal carcinoma, *the vagus and carcinoma of the thyroid*, bronchus and larynx, the recurrent laryngeal nerve

Benign tumors usually compress adjacent nerves without producing symptoms Ganglionic structures are also affected by adjacent cancer such as the superior cervical *sympathetic ganglions* involved by the superior sulcus tumor presenting a Horner s syndrome.

TUMORS OF THE NERVE SHEATHS INCLUDING NEUROFIBROMATOSIS (NEURILEMMIOMA)

Most tumors of peripheral nerves surprisingly do not arise from the nerve elements but rather from the tissues which sheath the nerves (Schwann cells neurilemma) Previous concepts claimed that *these tumors* were of nervous tissue origin, and they were thus labeled *neurogenic* tumors Because of the large amount of fibrous tissue intermingled throughout the malignant tumors the term *sarcoma* was affixed. The term *neurogenic sarcoma* has now been largely abandoned because it has been demonstrated that the tumors arise from the cells that cover the nerve elements—*the cells of Schwann*

—which, although ectodermal, have the propensity of producing connective-tissue fibers. Tumors arising from these cells, if benign, are termed *benign neurilemmoma*, encapsulated or diffuse (plexiform), if malignant, *malignant neurilemmoma* or *malignant schwannoma* If a combination of nerve tissue and fibrous tissue comprises the tumor, it is called a *neurofibroma* Von Recklinghausen's disease (multiple neurofibromatosis) represents an error of metabolism with a proclivity toward the formation of neuroectodermal tumors

Tumors of the Sympathetic Nervous System

The two other main groups of neoplasms arising from the peripheral nervous system are those which arise from the *sympathetic ganglionic cells* (ganglioneuromas, sympathicoblastomas) and those which develop from *paraganglionic cells* (paraganglioma, pheochromocytoma)

Another interesting tumor, which arises from a specialized type of paraganglionic cell, is the argentaffin (carcinoid) tumor of the gastrointestinal tract These occur most frequently in the appendix, less often in the small intestine and rectum They arise from the paraganglionic cells found in the bases of the crypts of Lieberkuhn, originally described by Kultschitzky and called argentaffin cells because of their affinity for silver stains Their precise function is not known Because the treatment of these tumors is in the realm of gastrointestinal surgery, they will not be discussed here

A small group of tumors of the peripheral nerves contain elements of ganglionic cell types Thus, ganglioneuromas have been reported in the neurofibroma of von Recklinghausen's disease The following have also been recorded, neuroepithelioma (radial nerve), medulloblastoma (sciatic nerve), medulloepithelioma (also called ependymoma), which recurs after excision but does not metastasize

Tumors of Central Nervous System Origin Occurring Peripherally

Similarly, tumors arise within the peripheral nervous system from misplaced tissue of the brain and spinal cord The most frequent sites of their occurrence are the orbit and the nose They may on occasion retain their attachment to the brain The benign variety are termed *ganglioglioma* (fibroglioma, nasal glioma) The malignant ones are designated olfactory *neuroepithelioma*, these infiltrate contiguous tissues, recur after excision, but do not metastasize Cures have been reported from combined surgical extirpation and postoperative irradiation

NEURILEMMOMA*

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* In collaboration with John

Schwann a derivative of the neuroectodermal cells of the neural crest, as demonstrated by Harrison According to Nageotte when myelin is present between the sheath and the axon the myelin probably comes from the axonal component. The histologic studies of Masson and Nageotte and tissue culture studies by Ingebrigsten, Gay and Murray and Stout would seem to demonstrate that the neuroectodermal Schwann cells can form reticulin fibers in vitro Because of the similarity of reticulin as produced by the Schwann cells and the fibrils produced by fibroblasts difficulty in separating malignant neurilemmomas from ordinary fibrosarcomas by histologic methods alone is apparent. In addition to the neuroectodermal derivatives and fibrous tissue, blood vessels, lymphatics and fat cells are found in the nerve trunks

Stone has demonstrated that in frogs the neural crest cell is multipotential and can produce tissue usually thought to arise only from the mesoderm. The role of metaplasia is verified by many instances Masson has found striated muscle cells in benign plexiform neurilemmoma, Wilson has noted bone formation Groth noted fat and cartilage in a neurofibroma excised from a patient with von Recklinghausen's neurofibromatosis and Stout has also observed cartilage and osteoid tissue in a recurring malignant nerve tumor of the brachial plexus These observations further illustrate that the neuroectoderm is multipotential and can give rise to various types of tissue usually considered mesodermal in origin. Ganglion cells have also been seen in neurofibroma. Epithelium lined cysts were described by Stewart as occurring in a peripheral nerve. Glandular elements producing mucus were noted by Foraker in a malignant neurilemmoma. These epithelial elements are probably ependymal in origin Furthermore, the ability of the Schwann cells to produce reticulin and connective-tissue elements accounts for the fibrous tissue contained in the common benign encapsulated and plexiform neurilemmomas Thus the components mesodermal and neuroectodermal elements of the nerve trunk, are capable of forming some type of tumor of a complex structure. The degree to which each tissue participates cannot always be accurately differentiated because of the very intimate relationship of these elemental parts of the nerve trunk. Most authors now agree that the neuroectodermal Schwann cell is the most active participant in the formation of the benign neurilemmoma, neurofibroma, and traumatic neuroma. The mesoderm is thought to participate only by providing the blood vessels and supportive connective tissue latticework in these lesions

The fact that a nerve is found incorporated in a tumor mass is not sufficient proof that the tumor arose from that nerve. Many malignant tumors of a sarcomatous type by their growth may surround and destroy major nerves However if the nerve contains or is incorporated in a tumor and the histologic structure is that of a malignant neurilemmoma, this would appear to be conclusive proof of origin in nerve tissue.

These neoplasms will be presented under the following headings

I Neurofibromatosis (von Recklinghausen's disease)
II Benign neurilemmoma (schwannoma, encapsulated and plexiform)
III Malignant neurilemmoma (schwannoma)

The neurofibromatoses (von Recklinghausen's disease) are a diffuse proliferation of nerve elements (Schwann cells accompanied by neurites) which probably represents a form of neuroectodermal dysplasia. This will be discussed first, as this inborn error of nerve metabolism offers leads concerning the pathogenesis and natural history of neoplasms of peripheral nerves

MULTIPLE NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

DEFINITION

Neurofibromatosis is a developmental diathesis of the neuroectodermal system with a strong tendency toward neoplastic proliferation (neurofibromas) The condition is most frequently inherited It may manifest itself in a variety of ways, varying from the simple tendency of pigmentation of the epidermis to a generalized widespread pathologic involvement of many portions of the nervous system (both central and peripheral nervous systems), other ectodermal structures such as the skin, various mesodermal structures—bones and connective tissues—and even certain entodermal structures, e g, certain portions of the intestine and appendix With the exception of a teratoid tumor, which consists of a localized abnormal growth involving the three germ layers, there is no disease process by which the human organism can be afflicted which produces abnormalities of the tissue derivatives of the three germ layers as does neurofibromatosis, so-called von Recklinghausen's disease

Von Recklinghausen described the entity which bears his name in 1882 Tilesius described this clinical syndrome in 1849 In 1908, Verocay elaborated upon the entity and introduced the belief that it represented but one manifestation of a generalized inborn ontogenetic error of the neuroectoderm This concept has been generally accepted Because of the frequent associated abnormalities which accompany the classic stigmas of neurofibromatosis, Yakolev and Guthrie suggested that the name *von Recklinghausen's disease* be changed to *congenital ectodermosis*, which would thus include the various manifestations of this disease entity

Some of the associated pathologic involvements of neurofibromatosis, in addition to the classic stigmas mentioned below, include certain neoplasms of the central nervous system such as meningiomas, acoustic neuromas, and optic nerve gliomas The classic stigmas include tuberous sclerosis, Lindau-von Hippel's disease, Sturge-Weber's syndrome, mental retardation from unknown pathology, abnormal nonneoplastic hypertrophy of the skin and bones, hirsutism, mesodermal tumors (lipomas, fibromas, and others), other congenital malformations such as hypospadias, spina bifida, cerebral meningocele, congenital defects of the fingers and toes. These may all be expressions of a broad nosologic developmental defect designated by the term *von Recklinghausen's disease*

INCIDENCE. GENETIC FEATURES

It has been estimated that neurofibromatosis occurs in about 0 05 per cent of the population It has been reported in all races, as well as in animals It has been shown that about half of the offspring of a parent with neurofibromatosis will present certain stigmas of this defect It may occur in several generations without a break Preiser and Davenport performed a comprehensive genetic study on 30 families with von Recklinghausen's disease and demonstrated that some evidence of multiple neurofibromatosis was present in 43 5 per cent of offspring According to Mendelian laws, this would accord von Recklinghausen's disease a dominant genetic characteristic Another interesting familial aspect of this disturbance is that the offspring may present the same type and location of le[illegible] do parents

A rather unusual [illegible]

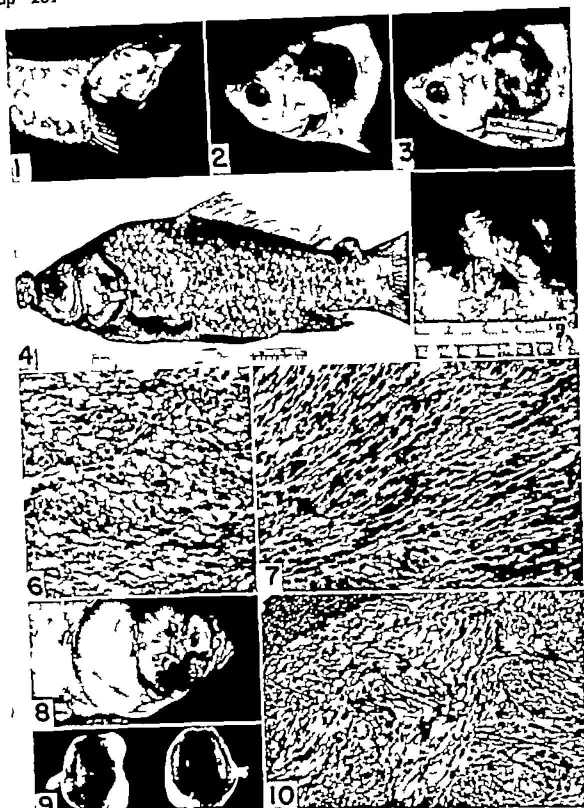


FIG. 370 Neurilemmomas and other stigmas of von Recklinghausen's neurofibromatosis in goldfish. *1* Neurilemmoma $3 \times 2 \times 2$ cm. on the caudal fin slowly increased in size over a period of 123 days. *2* A hemorrhagic malignant neurilemmoma on the trunk immediately behind the operculum. *3* Photograph of fish in *2* taken 25 days later shows rapid increase in size of the tumor *4* A neurilemmoma on the snout and another on the dorsum of the tail. *5* A pedunculated neurilemmoma which showed only slight local recurrence during 10 months following amputation at base of the pedicle. *6* Loose reticulated area from tumor in *5* resembling Antoni type B tissue of human neurilemmoma. *7* Different area from tumor in *5* showing fasciculate arrangement of cells and slight nuclear palisading, comparable to Antoni type A tissue of human neurilemmoma. *8* Ocular neurilemmoma. Large soft hemorrhagic tumor involving most of cheek directly behind eye cornea of eye thickened at its periphery by tumor tissue *9* Sagittal section through the eyes of fish in *8*, showing corneas greatly thickened by neoplastic growth. *10* Tumor replacing normal connective tissue of cornea in 9 (corneal epithelium in upper left hand corner) (*Courtesy* Dr Hans G Schlumberger and Cancer Research *12*,890 1952.)

serve the inherited characteristics of neurofibromatosis in fishes and thereby to study also the natural history of this entity was recently afforded Schlumberger An urban lagoon in Cleveland, Ohio, which had a surface area of 3–4 acres, had been stocked with goldfish 26 years ago, no goldfish had been added since In addition to the goldfish, there were blue-gill sunfish and large-mouthed black bass living in the same lagoon, but none of these fish showed any tumors, the only ones which showed tumors were the goldfish Schlumberger calls attention to the possible relation of the tumors and certain abnormalities in the fish to constitutional factors, and the similarity of the lesions to those encountered in von Recklinghausen's neurofibromatosis He found 144 tumors in 53 goldfish They were scattered over the surface of the body, mostly on the dorsolateral aspect of the head and trunk and caudal fin None of the tumors was encapsulated They were neurilemmomas, and seven were malignant Some of these fish also had focal pigmentation in the skin, and the nerve sheath tumors were pigmented in some They were associated, sometimes, with polycystic kidneys and buphthalmos Some of these were found in association with von Recklinghausen's disease, and attention was called to the fact that renal malformations have also been described in patients with von Recklinghausen's disease by F Weinstein Schlumberger found melanophores present in several of the neoplasms and said that the question of neural crest origin of both the pigment cells and the Schwann cells was considered All the tumors were subcutaneous with two exceptions

The fish were an isolated population, probably subjected to considerable inbreeding, and therefore had some genetic homogeneity Although 2-year-old offspring of apparently tumor-ridden fish were still free of tumors, a possible genetic background for both the tumors and the anomalies should be considered in the comparison with von Recklinghausen's neurofibromatosis in man

SEX

Von Recklinghausen's disease afflicts both sexes The male sex is slightly more frequently afflicted than the female

RACE

Von Recklinghausen's disease has been reported in all races In a report by Preston, Walsh, and Clarke, in which Negroes constituted 8 per cent of all patients bearing tumors, 7 per cent of the patients bearing multiple neurofibromatosis were Negroes This value fits in with other reports in the literature and indicates that there is no special predilection or immunity to von Recklinghausen's disease in the Negro

PATHOLOGY OF NEUROFIBROMATOSIS

Nervous-tissue overgrowth, an expression of von Recklinghausen's disease, may include any of the nervous-tissue constituents These can consist of neurilemma, neurites, ganglion and paraganglion cells, glia cells, cells of the ependymal layers lining the ventricles, cerebrospinal canal, and choroid plexus, mesodermal constituents of nerves (blood vessels, etc), specialized nerve endings, etc The primary pathologic involvement apparently consists of an hypertrophy and/or hyperplasia of the neurilemma. The dominant cell responsible for the defect here has been shown by the tissue culture studies of Murray and Stout to be the Schwann cell. The Schwann cells, which compose the neurilemma (nerve sheath), frequently reveal growth and tinctorial abnormalities in-

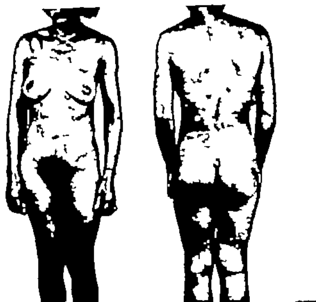


FIG. 371. A Negress, suffering from generalized neurofibromatosis, developed a malignant neurilemmoma of the popliteal space which was surgically excised. The patient remains free of evidence of recurrent neurilemmoma more than 5 years. (Vieta and Pack, Am. J Surg. 82:416 1951)

dicating an abnormal type of growth rather than orderly overgrowth. These neurilemmatous overgrowths may be either within the interior of the nerve, producing a grotesque form of the nerve, or in the perineurium, producing smaller or larger nodules affixed to the nerve covering, or a combination of these two growth features The result in such instances is a beaded, enlarged, twisted nerve.

Stout has described exact replicas of the Wagner Meissner tactile corpuscle as a pathologic feature. There is usually an associated edema of the tissues between the nerve fibers The nature of this edema and its mode of occurrence is not known, but it probably represents a defect of the mesodermal structures concerned with the proper metabolism of the chondroitin and mucoitin polysaccharides through the mediation of such enzymes as hyaluronidase, cholinesterase etc. (see p 158.) There is frequently an overgrowth also of the nerve fibrils Any of the other nerve constituents may contribute to the abnormal overgrowth. These are manifested by the following pathologic lesions which produce the clinical expressions that characterize this entity

1 *Tumors of nerve endings* These consist of tiny overgrowths of specialized subcutaneous nerve endings which vary from an individual subcutaneous nodule in certain regions to very numerous nodules in other locations The overlying skin is usually heavily pigmented.

2. *Café-au lait spots* These consist of an abnormal disposition of pigment (melanin) within the dermis Another evidence of an abnormality involving pigment metabolism is the frequent occurrence of pigmented moles.

3. Diffuse overgrowth of neurilemma of cutaneous and subcutaneous nerves produces a generalized thickening and hypertrophy of the involved tissue, which presents a very coarse, flabby appearance and may even hang in folds This is called *elephantiasis neuromatosa* This hypertrophy may occur also in bones, producing an abnormal skeletal overgrowth.

4. *Tumefactions of the nerves* These



FIG 372 Diffuse neurilemmomatosis in a young girl Note gigantism of arm, a result of both the plexiform neurilemmomas and overgrowth of bone

produce the typical plexiform neurilemmoma They are not encapsulated, which condition permits an expansile growth The plexiform neurilemmomas may occur as isolated tumors without the other stigmas of von Recklinghausen's disease They may occur in a nerve, which is otherwise apparently normal, in a patient suffering from von Recklinghausen's disease More frequently, however, they occur in deranged nerves which are diffusely enlarged and tortuous because of diffuse neurilemmatous overgrowth, and not infrequently the nerve may be the site of multiple plexiform neurilemmomas It is not unusual for these tumors to occur in regions of elephantiasis neuromatosa The plexiform neurilemmomas may condemn an entire nerve dermatome either by the coalescence of several growing plexiform neurilemmomas or by growing proximally along the nerve, invading the anterior and posterior nerve roots including the gangliomatous structures, and extending through the spinal foramina to infiltrate the spinal canal, producing thereby the neurologic symptoms of spinal cord involvement Sarcomatous transformation may occur anywhere within plexiform neurilemmomas (This is discussed later on page 599)

5 Tumors may occur primarily within the central nervous system Penfield believed these to be primarily *gliomatous tumors* These central nervous system tumors occur in about 5 per cent of patients with von Recklinghausen's disease, the signs and symptoms depending upon their size and location

CLINICAL MANIFESTATIONS

The various clinical manifestations of von Recklinghausen's disease can be best presented by describing the manner in which the different organs are afflicted

SKIN

1 *Café-au-lait spots* are the most common lesion of this entity They occur anywhere in the skin, no known factors determining their distribution They are most frequent on the trunk and arranged in an asymmetric manner They occur frequently also on the extremities and the face, but not as frequently or to as great a degree as on the trunk They rarely occur on the palms and the soles and have occasionally been reported as occurring in the mucous membranes They may on occasion be isolated, representing the only expression of the disease, or they may be so abundant as to give a brownish-blue hue to a large region (Fig 373) The exact pathology of this lesion has not been completely defined, although Tannhauser believes it to be a pathologic involvement of the cutaneous nerve or nerve ending, producing an increased pigmentation of melanin of the overlying epidermis

2 *Pigmented moles* are diffusely scattered throughout the skin and present

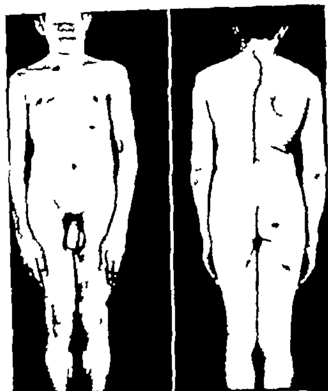


FIG. 373. Patient with generalized neurofibromatosis, showing bone deformities and café-au-lait spots.

the same morphology and distribution as pigmented moles without von Recklinghausen's disease.

3 *Cutaneous neurilemmoma* (*neurofibroma*) These tumefactions which are usually small, may vary in number from an occasional isolated tumor to such great numbers as to give a prickled appearance to the involved region. They are usually soft and asymptomatic. Davis and Pack have recently demonstrated that they present an increased response to pain stimuli. They are most frequently sessile but may be polypoid or pedunculated. They occur most frequently on the torso and extremities, and somewhat less often on the skin of the head and neck. They may occur on the plantar surface of the feet (7 per cent of 61 patients reported by Preston *et al*) or the palmar surface of the hands (5 per cent Preston *et al*) About 1 in 30 patients may present an associated Dupuytren's contracture, and it is believed that a relationship between these two diseases exists They may attain large size on occasion, with secondary ulceration and infection.

4. *Elephantiasis neuromatosa* described above, involves primarily the skin.

5 *Related pathologic manifestations of von Recklinghausen's disease* Fibroma molluscum represents a pure overgrowth of subcutaneous fibrous tissue and may occur anywhere in the body The anemic nevus of Vörner presents a pale-greyish appearance which fades on pressure and becomes more defined when the surrounding skin is irritated. It is believed to represent a congenital anomaly of the neurovascular system, producing localized vascular spasm (Sebastiani) Telangiectasis or frank cutaneous hemangiomas may not infrequently accompany neurofibromatosis Lindau von Hippel's and Stürge-Weber's syndromes (discussed later) also represent expressions of abnormalities of the vasculature associated with multiple neurofibromatosis

6. *Sebaceous adenoma* most fre-

involvement produces a variety of osseous abnormalities manifested clinically and radiographically as follows

1 When osteoclastic defects involve the shafts of long bones, there is a frequent irregularity of the periosteum and cortex. Tumors may extend exophytically from the bone. The appearance may be similar to that of a bone cyst. There may even be a periosteal osteoblastic reaction about the tumefaction. Such defects in the spine produce scoliosis kyphosis, or other severe deformities —the result of the vector of forces upon the vertebrae softened by the neoplasm An abnormal relaxation of the vertebral ligaments appears to contribute to the vertebral deformities

Another osseous entity associated with neurofibromatosis has been described this consists of congenital bowleg and pseudarthrosis of the tibia and fibula. Pseudarthrosis seems to be associated directly with intraosseous neurofibromas which cause pathologic fractures and retard or prevent bony union. The first *step in the process is the development* of a neurofibroma within the bone This weakens the bone so that the fracture is *caused by trauma so slight as* to escape the notice of the patient. The failure of the bone to unite is due to the presence of neurofibromatous tissue between the *fracture fragments Excision* of the neurofibromatous tissue with open reduction of the fracture and immobilization by internal fixation is the only method of treating this complication Without removal of the neurofibromatous tissue, bone callus formation between the bone fragments cannot occur Bone grafts may at times be indicated

2. The other osseous abnormality of von Recklinghausen's disease is gigantism of certain bones This is the osseous corollary of the ectodermal elephantiasis neuromatosa. An entire bone, such as the tibia or humerus may be massively enlarged, whereas *in other instances* a phalanx or even a portion of a phalanx



Fig 375 Congenital neurofibromatous macroglossia. (*Courtesy* Dr William W Ayers.)

may be diffusely hypertrophied. In a case reported by Hein and Reavas the second toe of the left foot was the manifestation of local gigantism. This was the only osseous involvement.

The association of osseous lesions and pigmentation invites speculation concerning the *possible interrelationship* between fibrous dysplasia, Albright's disease (fibrous dysplasia of bone epidermal pigmentation and sexual precocity) and neurofibromatosis There does *not appear to be any specific relation*ship Neurofibromatosis is primarily ectodermal, and fibrous dysplasia of bone represents essentially a mesodermal defect. Albright's polyostotic fibrous dysplasia presents mixed lesions The skin pigmentation represents a neuroectoder*mal defect*, whereas the osseous lesions are essentially mesodermal. Albright's syndrome may thus represent an ontogenetic defect nosologically located be*tween the pure mesodermal anomaly* of fibrous dysplasia and the generalized disturbance of von Recklinghausen's disease.

Congenital anomalies of the skeletal system are not infrequently associated with neurofibromatosis A hemivertebra has been described as an example of this condition. *Another example is* the vertebral defect associated with spina bifida occulta.

Inglis has written extensively on the relationship of *neurofibromatosis* and

local or general gigantism (acromegaly) He has described two levels at which the stimulus evokes the abnormal responses

First, the basic intrinsic factor is a primitive and comprehensive one which comes into play from the time of fertilization of the ovum to the time of appearance of the neural tissue in the developing embryo Its effect may be manifested in tissue derivatives of all germ layers

Second, the neural intrinsic factor is of neural origin and related to specific nerve-sheath tissue (neurilemma) Inglis states that in regard to the development of particular lesions of neurofibromatosis, it is often difficult to decide whether the responsible factor is at the neural level or the basic intrinsic factor level He discusses the three possible methods which may account for the local enlargement of an extremity, namely, abnormality in nerve supply, abnormality in blood supply (suggested by hemangiomatous formations in the involved region), and abnormality of hormonal control He presents evidence that none of these is responsible but that some fundamental abnormality accounts for all the defects Inglis reports several instances of local gigantism (macrodactyly) that are manifestations of neurofibromatosis He indicates that the local gigantism in several of his patients consisted of osteochondromatous tumors and believes that this defect, associated with neurofibromatosis, represents another manifestation of the intrinsic factor, either neural or basic, with a proclivity toward formation of chondromatous tumors

Of interest in this respect is local or partial acromegaly associated with generalized acromegaly Zondek in 1944 reported a 17-year-old girl whose gums, lips, and both jaws were thickened and coarse. Histologic examination of the wartlike proliferations of the gums and tongue revealed fibrous proliferation Inglis suggests that this condition corresponds to hypertrophy of the gums with general dwarfism described by Hutchinson, the gingival hypertrophy with marked hypertrichosis of the scalp, and the gingival and facial hypertrophy associated with neurofibromatosis described by Brain Each of these localized gigantisms are interpreted as due to manifestations of neurofibromatosis When local gigantism is associated with general acromegaly, it must be assumed that the former is an expression of neurofibromatosis and the latter a result of an abnormality of anterior pituitary hormone production Several such instances have been reported by Zondek, Guenther, Bauer, Allaria, and Sternberg It is possible that both abnormalities (neurofibromatosis and anterior pituitary hyperfunction) are defects produced at the basic intrinsic factor of Inglis

The bulldog scalp (cutis verticis gyrata) of one of Cushing and Davidoff's patients with acromegaly is interpreted by Inglis to be an expression of neurofibromatosis and related to other disturbances of hair growth such as the increased hairy patches related to nevi and the hairy tufts overlying spina bifida occulta described by Bland and Sutton Bulldog scalp in idiots has been described by Tredgold, and it is conceivable that both the idiocy and the scalp defect are due to neurofibromatosis

Other concomitant defects associated with acromegaly and expressions of localized gigantism include splanchnomegaly (alimentary tract, liver, etc), enlargement of the thymus, other lymphoid tissue and other endocrine glands (thyroid), syringomyelia, lipoid dystrophy, and others Inglis expresses the belief that none of these expressions of local gigantism, cutis verticis gyrata, syringomyelia, lipomatosis, etc , occurring in a patient with generalized acromegaly, is due to the anterior pituitary hormone, which is responsible for

the generalized acromegaly but all are manifestations of von Recklinghausen s disease. He expresses the belief that a fundamental basic intrinsic factor is the culprit responsible for the development of all the defects

OCULAR LESIONS

The ocular defects sometimes associated with multiple neurofibromatosis include palpebral neurofibroma, glaucoma, and retinal detachment. An interesting defect consists of primary optic atrophy associated with von Recklinghausen s disease. The atrophy is due most frequently to primary gliomas of the optic nerves and chiasm. There have been approximately 46 such cases reported Two instances of this condition occurred in uniovular twins. Peripheral neurofibromatosis occurs in about 10 per cent of patients with optic nerve or chiasmal tumors In 1940 Burke recorded that 446 such tumors had been reported in the literature with 46 being associated with generalized von Recklinghausen s disease Six case reports by Ira Cohen indicated good results in some instances in maintaining vision following excision of unilateral nerve involvement. He further described beneficial results following radiation therapy to the tumor in patients whose tumors were found to be inoperable.

OTHER ASSOCIATED SYNDROMES

TUBEROUS SCLEROSIS. This was described by Bourneville in 1880 in a 13-year-old girl afflicted with focal epilepsy acneform lesions of the face and nose, and idiocy The patient also had molluscoid lesions of the neck. Other lesions frequently associated with the entity include gliomas of the retina and rhabdomyomas of the heart and kidneys Skin lesions in addition to the acne include various angiomas and/or pigmented nevi.

Tuberous sclerosis occurs not infrequently in association with neurofibromatosis Other defects described with this combined syndrome include skull defects, spina bifida, and certain ontogenetic defects such as kidney agenesia.

The histologic evidence characteristic of the skin lesions consists of benign dermal neurilemmoma, and the characteristic central nervous system defect consists of regions of gliosis

Tuberous sclerosis of Bourneville may be but another manifestation of the congenital abnormality termed *multiple neurofibromatosis*

HEMANGIOMATOSIS. Dermal hemangiomas occur with von Recklinghausen s disease, and certain hemangiomas located elsewhere, usually in the brain, have been classified as follows

1. Lindau s syndrome, cerebellar cysts associated with a capillary hemangioma in its center Similar lesions may be found in the medulla oblongata or the spinal cord.

2. When hemangiomas of the retina also exist the entity is designated *Lindau von Hippel's disease* Additional defects of this disease syndrome consist of cysts or hypernephromas of the kidneys or adrenals and pancreatic cysts Cutaneous angiomas or nevi frequently occur A familial association exists in about 20 per cent of these patients

3 Stürge-Weber s syndrome of meningeal and facial hemangiomas may be associated with von Recklinghausen s disease

Lindau von Hippel s and Stürge-Weber s syndromes when associated with multiple neurofibromatosis present lesions of neuroectomesodermal developmental defects.

CLINICAL COURSE

The course of neurofibromatosis is often one of dynamic progression influenced by factors such as heredity the physiologic stresses manifested in

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Lesions

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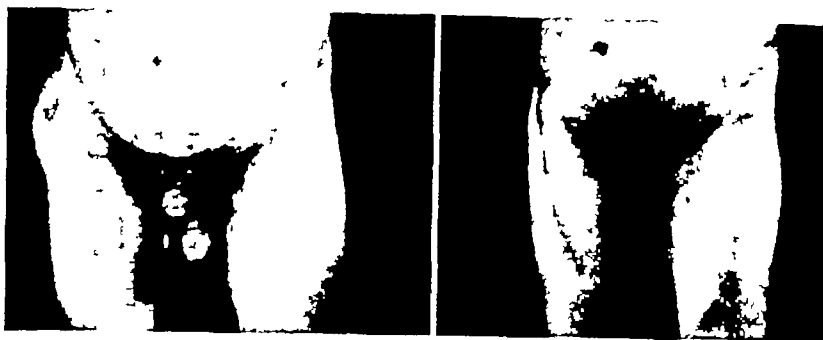


FIG 376 Multiple malignant neurilemmomas in a patient with neurofibromatosis (*Left*) Malignant neurilemmomas of right upper thigh and shaft of penis (*Right*) Photograph of the patient 2 months after surgical excisions He has now been cured of these neurilemmomas for 18 years Previously, a malignant neurilemmoma of the right upper arm had been excised and he has been cured of this tumor for 24 years

adolescence by growth, and the probably unknown specific factors engendered by puberty, pregnancy, and the menopause

TREATMENT

In patients with the classic generalized form of the disease, operative treatment has little to offer, but the patients should be kept under careful observation to note excessive growth of certain tumors or other complicating features (malignant degeneration) which may be amenable to surgical intervention

Pregnancy may provoke dramatic changes Whereas before pregnancy the patients may exhibit only the abortive type of disease, with pregnancy many new lesions may appear, and those already present may increase markedly in size, as if there were an exacerbation of the disease Each succeeding pregnancy will evoke a similar response Sterilization may be considered when progression of the disease may cause serious involvement of the central nervous system or malignant degeneration of one of the many plexiform neurilemmomas Where there is an exacerbation of the disease with pregnancy, most of the offspring will have the disease, and curiously where there is no such exacerbation, there is a good chance the offspring will be spared this stigma

Complications arising with the generalized type of disease calling for surgical intervention are: (1) increased size of the tumor which causes pain or interference with activity, (2) cosmetic disfigurements, (3) hemorrhage into, or infection of, a large pachydermatocele, (4) rapid progression in size when the question of transformation to malignant neurilemmoma is present When the disease appears in its abortive type, complete eradication of the presenting lesions is possible by surgical treatment The isolated benign plexiform neurilemmomas may be extirpated with relative ease depending upon the extent of the pathologic process However, many of the larger isolated plexiform masses will appear infiltrative because of their tendency toward diffuse distribution along tissue planes Even though they are benign, complete excision must be effected or local recurrence is the rule Any subsequent procedure is more difficult and more destructive

Surgical removal of small tumors for microscopic study or for the cosmetic effect has not been followed by increased growth phenomena Some authors have stated that the removal of a malignant neurilemmoma or even those which are benign appears to stimulate other neurilemmomas to undergo malignant transformation Because of these

statements some have felt that interference with the benign tumors occurring in von Recklinghausen's disease is unwarranted, as surgery or any other type of treatment may be the stimulus to malignant transformation of tumors locally excised and those occurring elsewhere. In a large experience with the treatment of many benign nerve tumors, the authors have not seen any cases in which excision of a benign tumor was followed by recurrence in a malignant form. Therefore, if there are indications for surgical treatment of tumors in von Recklinghausen's disease, a hands-off policy because of the above unproved concept is not warranted. Most patients with von Recklinghausen's disease die with the disease and not from it.

Each surgical problem must be judged on its own merits, and each operation must be individualized to meet that particular situation. When conglomerate irregular masses of plexiform neurilemmoma within the subcutaneous tissues require extirpation, they can be readily dissected and no nerve repair is necessary. When, however, similar masses are encountered where the involvement of major nerve trunks would necessitate their sacrifice and repair by nerve suture, the surgical procedure should not involve sacrifice of these nerves unless an accurate diagnosis of malignant degeneration is obtained. Whenever the overlying skin is pigmented or takes the form of a pachydermatocele, portions of it must be excised along with the underlying neuromatous process to obtain a good cosmetic result. In principle then, no major motor nerve trunk should be sacrificed in the treatment of the benign plexiform neurilemmomas of von Recklinghausen's disease. If the question of whether the process is benign or malignant arises at an exploratory procedure, frozen section pathologic diagnosis may give an answer and the indicated procedure may then be extirpation of a malignant neurilemomma.



Fig. 377 Showing the severe osseous deformities often associated with von Recklinghausen's neurofibromatosis. A large malignant neurilemmoma involving the right shoulder and back had been resected previously

Hemorrhage into pachydermatoceles, although rare, does occur and should be recognized if there is a rapid increase in the size of these masses and if signs of blood loss are noted. The tendency is for the hemorrhages to occur intermittently from large dilated veins within the friable tissue to form a large hematoma. The lesion must be extirpated completely in order to control the hemorrhage.

Occasionally due to pressure necrosis of the skin over a sacculated plexiform neurilemmoma, infection of the gelatinous-appearing tumor-tissue contents will result. With infection the mass will continue to discharge necrotic material and the chronic inflammatory process is only eradicated by a resection of the mass after suitable preparation with various antibiotics has brought the spreading inflammatory reaction to a quiescent stage.

The treatment of lesions of von Recklinghausen's disease which have undergone malignant transformation is considered in detail in the discussion of the treatment of malignant neurilemmoma. This is a most serious complication, and

the incidence of malignant transformation varies with different authors who report on this syndrome. Garre noticed a sarcomatous change in 12 per cent of his patients. Courvoissier recorded it in 6.5 per cent of his 800 patients with neurofibromatosis. Charache stated that about 75 cases had been reported up to 1940. Hermann recorded 4 such patients, 2 were brothers. In our experience, approximately 10 per cent of patients with neurofibromatosis developed malignant neurilemmomas. Malignant melanoma is occasionally associated with neurofibromatoses.

BENIGN NEURILEMMOMA

Benign neurilemmoma occurs usually as an encapsulated solitary neoplasm arising from Schwann cells which grows in an expansile manner. Occasionally it forms a component of neurofibromatosis.

Early tumors are noted as solid projections within the epineurium, but as growth distends and expands the nerve fibrils, the tumor may be found surrounded by spokelike, thinned nerve fibers, or the nerve may course along one of the surfaces of the neoplasm. They are most frequently eccentric in relation to the nerve but on occasion may be located within the nerve.

They may occur anywhere within the central (acoustic neuromas) or peripheral nervous system. They are solid neoplasms when small, but as growth progresses it is not unusual for the solid portions of the tumor to be punctuated by smaller and larger regions of hemorrhagic necrosis.

They have been described in all ages and races and in both sexes, with no special predilection. Their cause is not known, and the marked histologic difference between this tumor and traumatic neuroma would serve to exclude trauma as an etiologic agent.

SYMPTOMATOLOGY. DIAGNOSIS

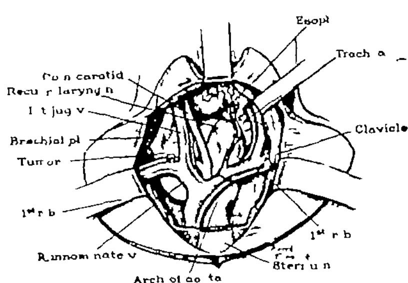
Their symptoms and signs are few. Smaller tumors are usually asymptomatic, but as the tumor grows and compresses adjacent nerve fibrils, sensory or motor symptoms in the regions innervated by the nerve develop. Encapsulated neurilemmomas of the extremities are usually small (3 to 5 cm. in diameter) because their superficial location exposes them to view or nerve-pressure symptoms incite diagnostic measures and subsequent treatment. Those arising in the mediastinum (Fig. 378) or retroperitoneum, however, at times grow to large size but remain asymptomatic because of the anatomic freedom offered by the mediastinum to the unhampered development of the neoplasm. The histologic appearance is important from a therapeutic standpoint. Inasmuch as these tumors are benign (no verified malignant transformation of a benign encapsulated neurilemmoma has been observed), conservative surgical measures may be utilized for their removal. In fact, severance of a major nerve is practically never indicated. Exceptions, of course, may occur.

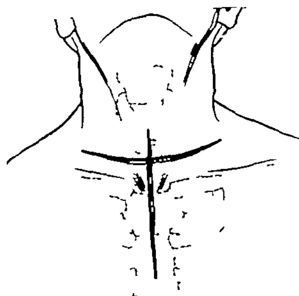
It is, accordingly, mandatory to establish an accurate preoperative diagnosis.

The nature of the neoplasm can be suspected by its location in the lateral portions of the neck, the posterior mediastinum, or the flexor surfaces of the extremities in relation to a peripheral nerve.

A correct diagnosis by means of an aspiration biopsy has been reported by several authors, but if this method should fail, then a histologic examination of a frozen section obtained from a small portion of the exposed tumor will establish the diagnosis.

The morphologic appearance is typ





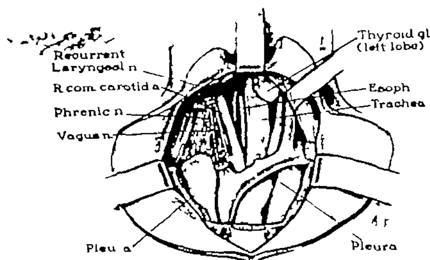


FIG. 378. (*Upper*) A large neurilemmoma involving the mediastinum which was surgically excised. (*Middle*) The incision utilized to gain access to the superior mediastinum and which permitted excellent exposure for the successful extirpation of the neurilemmoma shown in upper figure. (*Lower*) Postoperative illustration showing the anatomic structures which were involved. (*Courtesy* Dr John O Vieta.)

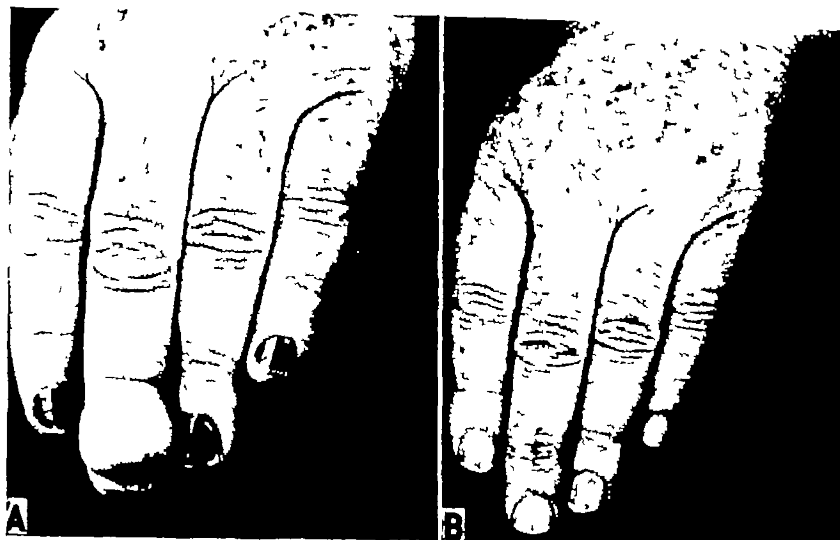


Fig 379. *A* Benign neurilemmoma of the middle finger *B* Appearance after surgical excision

ical There is always a capsule, within which is an intermingling of the two distinct types of cellular structures A solid mass of cells with palisading of the nuclei and a grouping of the fibrils to mimic an attempt at organoid formation (Verocay body) is observed This type of tissue, called Antoni type A, is interspersed with Antoni type B tissue consisting of a loose fibrillar structure, cystlike in appearance, in which Schwann cells are scattered about Numerous cysts are present Neurites are rare or nonexistent, at times fibrils from adjacent nerves penetrate the tumor Hemosiderin pigment is frequently present from numerous blood vessels, and lipoid-containing cells are noted in mediastinal neurilemmomas

Sometimes pleomorphism of cells exists and this feature has erroneously resulted in a diagnosis of a malignant tumor and a more radical type of treatment practiced

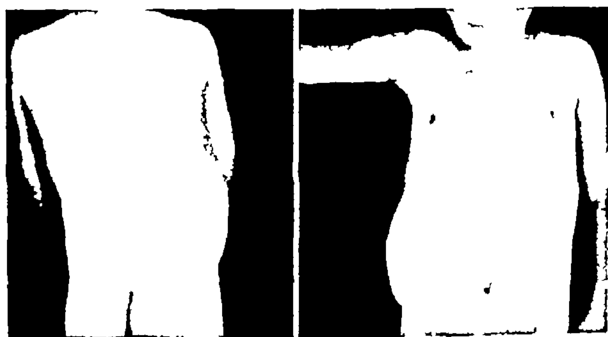


Fig 380 Benign retroperitoneal neurilemmoma in a child (Plexiform type) Removed by serial segmental excisions

Benign encapsulated neurilemmomas are rarely associated with von Recklinghausen's disease In Ehrlich and Martin's series of neck neurilemmomas, none had stigmas of neurifibromatosis Stout, however, believes that about 18 per cent occur in patients with neurofibromatosis Godwin *et al* reported that the incidence of encapsulated neurilemmoma in patients with von Recklinghausen's disease seen at Memorial Hospital is less than 18 per cent

INCIDENCE

Stout recorded 244 benign neurilemmomas in 1935 These tumors were diffusely distributed throughout the peripheral nervous system but were most abundant in the flexor surfaces of the extremities

There have been about 19 neurilemmomas recorded in the brachial plexus (Godwin) Ehrlich and Martin reported 12 instances in the neck, and two series of neurogenic tumors in the thorax include 20 neurilemmomas out of 18 total cases (Ackerman) and 12 neurilemmomas out of a total of 24 patients reported from Memorial Hospital

Ackerman and Taylor describe another form of neurilemmoma which they

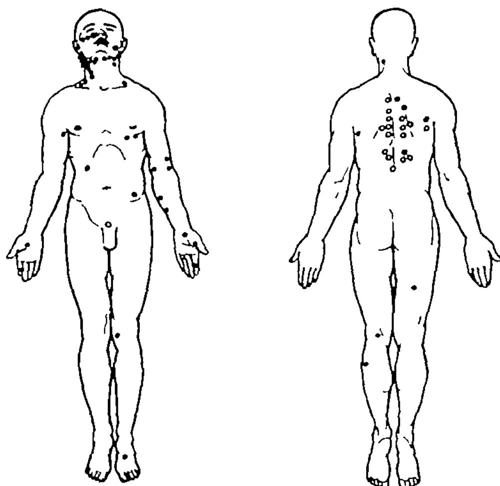


FIG. 381 Scattergram showing regional distribution of benign encapsulated neurilemmoma.

call *ancient neurilemmoma* because of the presence of fibrous nodules which they believe occur from hyalinization of diffuse overgrowth of cells blood vessels and connective-tissue cells. These tumors are solid with no evidence of necrosis Ten such tumors were described in the mediastinum, and their treatment is the same as for the usual neurilemmoma

TREATMENT

Encapsulated neurilemmomas should always be treated by conservative measures excising the tumor with its capsule from its nerve of origin The approach depends upon the nerve which is involved and at times may be rather difficult. Ehrlich and Martin report a case of an encapsulated neurilemmoma arising in the brachial plexus and which presented in the cervical region. As a general rule an incision over the tumefaction will permit proper exposure The neurilemmoma will then be visualized in one of three positions in relation to its nerve of origin

1. It may present as a fusiform swelling involving the entire nerve. This usually occurs in the smaller nerves whose sacrifice does not produce significant disability In such instances the treatment is complete excision of the tumor including the nerve.

2. The tumor may be eccentrically placed with the nerve coursing over one of the surfaces In such instances the

neurilemmoma can be dissected free from the contiguous nerve

3 The tumor may be centrally placed within the nerve This occurs usually in larger nerves and the treatment consists of separating the nerve fasciculi and dissecting the tumor free from its origin If the capsule cannot be dissected free, the tumor may be enucleated Although this practice violates the usual tenets of cancer surgery, the observation that recurrences following this procedure are extremely few and that malignant degeneration of an encapsulated neurilemmoma has not been noted warrants the conservative procedure rather than the sacrifice of an important nerve

The pitfall lies in the mistaken clinical belief that these neoplasms are malignant Such errors result from a false impression gleaned by gross inspection of the tumor or from misinterpretation of an aspiration biopsy of these tumors Several such instances have been reported in which valuable nerves were sacrificed needlessly A rather interesting report by Godwin consists of three cases of benign encapsulated neurilemmomas in patients who had also been treated for papillary thyroid carcinoma The neurilemmomas could easily have been mistaken for lymph node metastases from the thyroid cancer (They were in most cases) Such cases emphasize the need for careful examination of any tumor regardless of the patient's previous clinical history

THE DUMBBELL (HOURGLASS) TUMOR

The so-called dumbbell (hourglass) tumor is included in this section on neurilemmomas because the majority of them are neurilemmomas, although some may arise from the sympathetic nervous system This group of neoplasms presents one of the most dramatic clinical responses to surgical intervention The clinical entity of a benign neoplasm producing malignant and disastrous neurologic symptoms by pressure against the spinal cord presents an intriguing surgical problem Most may be surgically extirpated with complete or almost complete relief of the symptoms caused by pressure against the spinal cord To neglect operating upon a patient suffering from this complex would indeed be calamitous The dramatic importance of recognizing these neoplasms early and attacking them boldly warrants emphasizing their natural history

The tumor derives its name from the dumbbell or hourglass appearance caused by an expanded intraspinal portion, a narrowing of that portion within the intervertebral foramen, and another expanded extraspinal segment

This type of neoplasm has been commented upon since the middle of the last century Weber in 1856 described the syndrome of an intra- and extracordal mass connected by a slender, rodlike, intervertebral foraminal, neoplastic connection which produces the dumbbell, or hourglass, appearance Virchow in 1899 described an hourglass tumor which was resected Antoni in 1920 and Heuer in 1929 presented the historic development of knowledge concerning the natural history and treatment of this interesting oncologic entity Since then many reports have appeared

That they are not uncommon is indicated by the figures from the Mayo Clinic (Love and Dodge) where, of 1000 spinal cord neoplasms treated between 1914 and 1951, 290 were neurilemmomas, and 60 of these were of the dumbbell variety Naffziger and Brown reported 15 dumbbell tumors from the University of California Heuer reported 64 instances recorded to 1929 but believed this represented a fragment of the true incidence The majority were benign neurilemmomas

Although most of the dumbbell neoplasms are neurilemmomas which arise from tissues about the spinal cord, other dumbbell tumors are ganglioneuromas or occasional neuroblastomas More rarely chordomas or mesodermal tumors (fibroma, lipoma, osteoma, or rhabdomyosarcoma) produce this syndrome. Dumbbell tumors may also arise from the spinal cord itself (gliomas ependymomas meningiomas etc.) Other causes for the dumbbell syndrome are certain malignant tumors arising from tissue adjacent to the vertebral column and secondarily invading the cord congenital enlargement of an intervertebral foramen tuberculosis hydatid disease, and rarely echinococcosis

CLINICAL FEATURES

Most dumbbell neurilemmomas occur within the middle-aged adult bracket (30 to 50 years) with a gradual and almost equal decrease in incidence in the decenniums preceding and following this age group Although rare they may occur in children most dumbbell tumors of children are ganglioneuromas which are usually diagnosed within the first few years The dumbbell ganglioneuromas like the neurilemmomas, are benign but metastases have been described. Williamson and Boley's 3-year old child acquired cervical metastases from a ganglioneuroma in the region of the fifth thoracic vertebra The metastases revealed highly differentiated, benign appearing ganglioneuromatous cells similar to those of the primary tumor In several reported cases (Berner and Miller) metastases from a differentiated ganglioneuroma revealed evidences of anaplasia simulating a neuroblastoma. Capaldi reports an interesting dumbbell ganglioneuroma which at first was thought to have metastasized to the axilla and neck but was later found to be an extension of a primary thoracic ganglioneuroma.

The neurilemmomas may occur anywhere in the spinal tract, from the highest cervical to the lowest sacral region, and may produce symptoms due to compression of one or several segments of the spinal cord in addition to symptoms produced by compression against extraspinal structures An interesting group of central nervous system tumors are those craniospinal tumors which extend through the foramen magnum and acquire the dumbbell shape from intracranial and intraspinal expansions The 60 dumbbell neurilemmomas reported by Love and Dodge involved most frequently the cervical and thoracic locations (26 cervical and 21 thoracic neoplasms) There were 11 lumbar tumors and only 2 occurred in the sacral region. The right and left sides were equally involved (28 right and 32 left)

The symptoms depend upon the extent and direction of growth The exact site of origin frequently cannot be determined as they may originate from one of three sites (1) They may develop intraspinally and extend through the intervertebral foramen outwardly In such instances the symptoms due to cord compression will dominate (2) They may arise from anterior or posterior spinal roots in the paravertebral location The earliest symptoms in these cases may be due to pressure against extravertebral structures (3) They may arise from the nerve in the intervertebral foramen extending in both directions to compress both the spinal cord and the paravertebral structures It has been postulated that the dumbbell neoplasms may be congenital, deriving their shape from indentation in the midportion caused by the developing vertebra

The most frequent initial symptom is usually neurologic, such as numbness and weakness of an extremity or pain. The symptoms of course, depend upon the location and size of the neoplasm varying from absence of symptoms to complete paraplegia. Roentgenologic ex

amination will reveal a variety of abnormalities consisting of one or more of the following enlargement and/or erosion of the intervertebral foramen, erosion of the vertebral body or the vertebral portion of the ribs, on occasion, a paraspinal mass with or without calcification In the series by Love and Dodge, the most characteristic roentgenographic appearance was an enlarged, smoothly eroded intervertebral foramen (as would be expected to be caused by a benign neoplasm), producing pressure molding rather than actual infiltration (as might result from a malignant neoplasm)

Spinal puncture with manometric studies (Queckenstedt test) will reveal evidence of subarachnoid block in about half of the cases Spinal fluid protein is frequently elevated above 100 mg per cent When the clinical picture and the above-mentioned tests are not conclusive, contrast myelography can be diagnostic

TREATMENT

The balanced surgical care of a patient bearing a dumbbell neoplasm requires a correlated effort by the neurosurgeon and one of his surgical colleagues Those neoplasms in which the bulk of the tumor exists within the spinal canal, with but a small part extending extravertebrally, can best be treated by a hemi- or total laminectomy Those with a large extraspinal component will necessitate resection of the contiguous tissues, which depends upon the size and location of the neoplasm

Dumbbell Tumors in the Cervical Region

The treatment of these dumbbell-shaped neoplasms depends upon the size of the neoplasm and the degree to which contiguous structures are anatomically compromised by it It is usually necessary to remove them by two separate incisions The decision of whether to remove the cervical portion or the intraspinal portion depends upon the existing situation in a given patient and the preference of the surgeon Love and Dodge favor the laminectomy first with excision of the intraspinal portion of the neoplasm They believe that if the cervical portion is removed first, a danger from extradural hemorrhage and edema extending up the spinal cord, with resultant damage to normal structures, may develop Another anatomic pitfall in resecting dumbbell neurilemmomas is the presence of the vertebral artery Avoidance of either sacrifice of or hemorrhage from the vertebral artery is of prime importance during the excision of the intraspinal portion of the neoplasm The resection of the extraspinal portion of the tumor follows all the tenets of head and neck surgery For more detail, see Chapter 26

Thoracic Dumbbell Tumors

The adequate control of dumbbell neoplasms within the thorax requires careful surgical cooperation The question of whether the laminectomy or the thoracotomy should be performed first is answered differently by different surgeons At the Mayo Clinic the laminectomy is performed first If the extraspinal protrusion of the neoplasm is small, the neurosurgeon thoracotomizes the patient and resects the neoplasm at one surgical séance For larger extraspinal neoplasms, the thoracotomy is performed about ten days postlaminectomy If a chest mass unsuspected of being a dumbell tumor is first excised, the patient should be carefully watched for signs of spinal cord involvement due either to hemorrhage or edema about the intravertebral neoplasm If this should occur, an emergency decompression is performed Kay favors a primary thoracotomy, because in several cases in which he had initially performed a laminectomy, he found diffi-

culty in distinguishing between tumor tissue and scar tissue during the thoracotomy performed two weeks later He further believes that removal of portions of the vertebra with enlargement of the spinal foramina during the initial thoracotomy favors resection of the neoplasm during the subsequent laminectomy At times it may be necessary to resect portions of the posterior chest wall for this group of tumors

Dumbbell Tumors of the Abdominal and Lumbar Regions

Here again the question of laminectomy or excision of the extraspinal portion depends upon the preference of the individual surgeon The surgical handling of the extraspinal portion is the same as that discussed in the chapter dealing with retroperitoneal tumors, as many of these neoplasms are retroperitoneal. Two incisions are usually necessary one for the laminectomy and another for the extraspinal portion. The choice of incision depends upon the anatomic situation in a given case.

It is emphasized that whenever one is attempting surgical resection of a neoplasm in a paravertebral region, the possibility of a dumbbell tumor should be considered At times the connecting pedicle between the intra and extraspinal portions may be slender and could be inadvertently transected In such instances spinal cord symptoms will invariably occur and a paravertebral recurrence develop

It is conceivable that as more experience is gained, both the intra and extraspinal portions of these neoplasms can be resected at one surgical sitting by an appropriate surgical team.

PROGNOSIS OF DUMBBELL TUMORS

Neurilemmomas are surprisingly benign despite the malignant clinical sequelae which may result from their presence Adequate surgical resection will cure the vast majority of these neoplasms Good functional recovery from compression phenomena to the spinal cord will usually occur after the neoplasm has been extirpated. A period of one to three years may be needed to effect the nervous-tissue repair Of the 60 patients with dumbbell neurilemmomas reported from the Mayo Clinic, 48 of the tumors were removed at a single operation and 12 required a two-stage operation. There were six operative deaths (10 per cent mortality) prior to 1933 and none since. Most of the patients had good results following operation, with only two having poor functional recovery There were only three recurrences

Dumbbell ganglioneuromas carry with them a poorer prognosis Thus the patients reported by Rapp (4-year-old male) Naffziger and Brown (7 year old male) Stout (2½ year-old male) Eden (23-year old male) and Williamson and Boley (3-year-old female) all succumbed shortly after operation for dumbbell ganglioneuromas These tumors although benign, tend to be more infiltrating, and the large size attained by them makes complete extirpation difficult. Dumbbell neuroblastomas are malignant neoplasms and usually carry with them a poor prognosis In a case of Cushing and Wolbach, a malignant tumor biopsied in a paraplegic male infant aged 1 year and 9 months was explored ten years later and an intraspinal extradural ganglioneuroma was successfully removed. It was postulated by the authors that a dumbbell malignant neuroblastoma had reverted into a benign ganglioneuroma. Eden reports a 23-year old male who presented a history of a partial paralysis at the age of 5 which subsided spontaneously and a chest mass visualized roentgenographically Eighteen years later paraplegia recurred, and the patient died following thoracotomy Autopsy revealed a dumbbell tumor traversing several intervertebral foramina The tumor was a gan

glioneuroma, and it has been postulated that it may have been an original neuroblastoma which reverted to a ganglioneuroma similar to the patient of Cushing and Wolbach Another successful resection of a dumbbell ganglioneuroma was reported by Sames in 1950 in a 3-year-old paraplegic female who had an initial laminectomy and a subsequent thoracotomy The paralysis subsided, and the patient has remained well over five years A successful resection of a dumbbell neuroblastoma has been reported by Williamson and Boley

MALIGNANT NEURILEMMOMA*

The authors' series of 31 patients having malignant neurilemmomas will be discussed in detail as a means of demonstrating the natural history, methods of treatment and therapeutic accomplishments

The tumors labeled *malignant neurilemmoma (schwannoma)* are those which formerly were incorrectly catalogued as *neurogenic sarcoma*

CLINICOPATHOLOGIC SUBDIVISION OF MALIGNANT NEURILEMMOMA

The series is divided into two clinicopathologic groups. Group I, malignant neurilemmoma with stigmas of von Recklinghausen's neurofibromatosis, and Group II, malignant neurilemmoma without stigmas of neurofibromatosis These groups are analyzed separately to note if any difference in natural history or prognosis exists

Group I totals 11 patients (7 females and 4 males) Their average age was 32 years, with females averaging 28 years and males 39 years In Group II there were 20 patients, 9 females, and 11 males The average age was 42 years, females averaging 37 years and the males 44 years It thus appears that females with von Recklinghausen's disease more frequently develop malignant nerve tumors at an earlier age than the other patients In the female with generalized neurofibromatosis, the periods of puberty, pregnancy, and the menopause are definitely known to affect the clinical course of the disease What relationship these physiologic processes in the female had to the primary occurrence of malignant neurilemmoma could not be deduced from any evidence found in these clinical records In one patient, however, recurrence developed during pregnancy, and the tumor grew with explosive rapidity (Figs 56, 57, 58, and 378)

We repeat Hosoi's often quoted statement "In some cases the extirpation of a malignant tumor, or even a benign one, appears to stimulate another neurofibroma distally located to undergo sarcomatous transformation" Because of this statement, many have believed that interference with benign peripheral tumors is unwarranted, as extirpation or any type of treatment may be the stimulus to formation of a malignant tumor As stated above, in a large experience with the treatment of benign nerve tumors, we cannot recall any case in which excision of a benign tumor was followed by later development of a malignant tumor

DISTRIBUTION OF MALIGNANT NEURILEMMOMA

In Figure 382 the distribution of the 31 cases of malignant neurilemmoma is shown graphically The sites of predilection are the extremities, with the upper extremities more frequently involved The tumors may occur anywhere We have not encountered any in the abdominal cavity proper Ransom and Kay have reported several abdom-

* In collaboration with John O Vieta

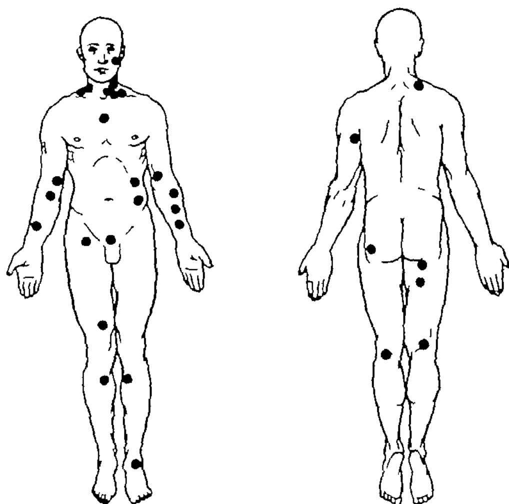


Fig. 382. Scattergram showing regional distribution of malignant neurilemmoma. Note similarity of distribution of malignant neurilemmoma and benign encapsulated neurilemmoma (Fig. 381) (Vieta and Pack, Am. J Surg. 82:416 1951.)

inal neoplasms of neurogenic origin. Likewise, Adrian, Kohta, and Hartmann have noted cases of malignant nerve tumors of the intestinal tract. Those found retroperitoneally about the lumbosacral plexus in the authors experience have extended into this region from tumors originally situated in the buttock or femoral triangle

The tumors of our series were located as follows arm three patients forearm, five patients thigh and buttock, five patients popliteal space two patients back, five patients brachial plexus, three patients leg, two patients supraspcapular fossa one patient mediastinum one patient abdominal wall, two patients foot one patient and perineum, one patient.

In frequency of involvement, the major nerve trunks demonstrated in 17 patients were median, five, sciatic, two ulnar two radial, one brachial plexus, three femoral, one and perineal nerve, three. Malignant neurilemmoma originating in plexiform neurilemmoma or elephantiasis neuromatosa was noted in 12 cases In two patients we were not able to demonstrate grossly the nerve from which the tumor originated One of these had von Recklinghausen's disease the other did not.

PATHOLOGIC ANATOMY

As previously stated, the majority of these tumors develop along a recognized peripheral nerve. In the solitary form of malignant neurilemmoma the growth may remain encapsulated or confined

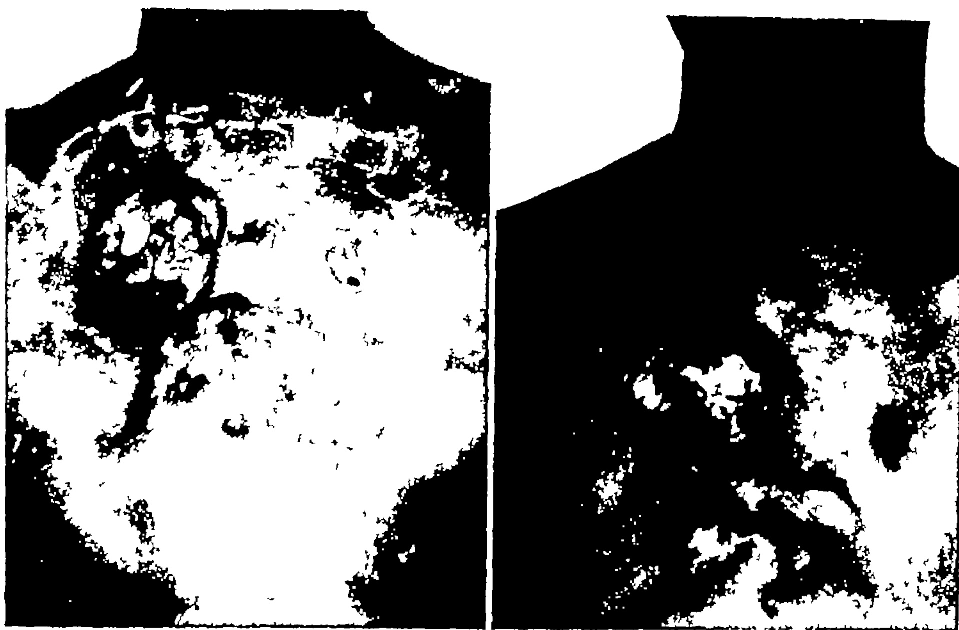


FIG 383 (*Left*) Malignant neurilemmoma of chest wall treated by surgical excision and irradiation (*Right*) Appearance 11 years later. This patient is living and well 24 years after treatment The original therapy was started before surgical resection of the chest wall was generally done



FIG 384 (*Left*) Diffuse malignant neurilemmoma of the lower leg (*Right*) Dissected specimen after amputation, demonstrating the intimate attachment of the neoplasm to all contiguous structures

within the nerve sheath, expanding it or forming a round or fusiform mass whose shape is determined by the denseness of the surrounding tissue in which the nerve tumor is expanding These solitary tumors may reach large proportions without showing any noticeable gross infiltration of surrounding tissues It is evident that they are grossly encapsulated, but the capsule is in reality a pseudocapsule Points at which this "capsule" adheres to muscle, fascia, bone, or vessels can usually be shown histologically to contain viable tumor

cells These regions of adherence are of microscopic infiltration and are the foci which serve as nidi for local recurrence if the tumor is "shelled out" of its "capsule."

These solitary tumors tend to grow along the nerve trunk more than into the tumor bed The nodules may how ever represent a multicentricity of ori gin for some malignant neurilemmomas, as outlined by Geschickter and Stewart. It can be demonstrated histologically that extension may be by continuity of growth by way of the intraneural peri neural, and perivascular lymph spaces. It is believed that growth along such routes may be one reason for the frequency of recurrences Stewart and Copeland stated that the malignant nod ules occurring in the nerve proximally or distally from the main mass original ly or as "recurrences" represented a new tumor arising in a condemned seg ment of the nerve Thus multicentricity of origin, growth by continuity along the nerve, tumor embolization along lymphatics or seeding of the operative region with neoplastic cells may all be factors concerned in local persistence or recurrence of the disease. Growth by continuity along the nerve and embolization along lymphatics account for some of the local recurrences in locally excised or amputated specimens in that the parent nerve is not sacrificed suffi ciently proximal or distal to the local growth to remove the neoplastic proc ess extending microscopically within the nerve trunk. Although tumor cells are occasionally seen in the lymphatics coursing with the nerve, the authors have not demonstrated regional lymph node metastases from the tumors although others on occasion have observed lymph node involvement both early and late in the course of the disease Encapsulated satellite nodules dis tant from the main tumor may be seen as bulbous enlargements along the course of the main nerve involved or

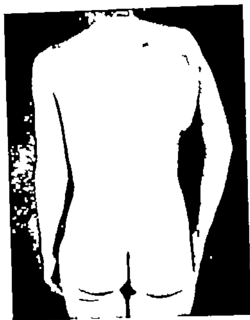


Fig. 385 Extensive malignant neurilemmoma of shoulder Note café-au-lait spots.

may occur along its proximal or peripheral branches

The gross extent of the tumor can often be delimited by observing the thickening and edematous appearance of the perineural tissue. It is perplexing to note how a nerve may seemingly be grossly destroyed by the tumor· a normal-appearing nerve is seen entering the tumor and distally reappearing in normal gross configuration. It is impossible to dissect the nerve through the tumor mass yet almost normal function of that nerve may be preserved as the axis cylinders are displaced but are still intact. This feature is equally evidenced in those malignant neurilemmomas originating in plexiform neurilemmomas In this latter group the tumor grossly appears to be of an infiltrative nature, but this is due to the fact that the plexiform variants themselves appear infiltrative because of their tendency toward diffuse distribution along natural tissue planes.

In the malignant neurilemmomas originating in plexiform neurilemmomas interspersed with interlacing strands of firm white tissue showing tortuous bulbous enlargements of neuromatous peripheral nerves, there are lob

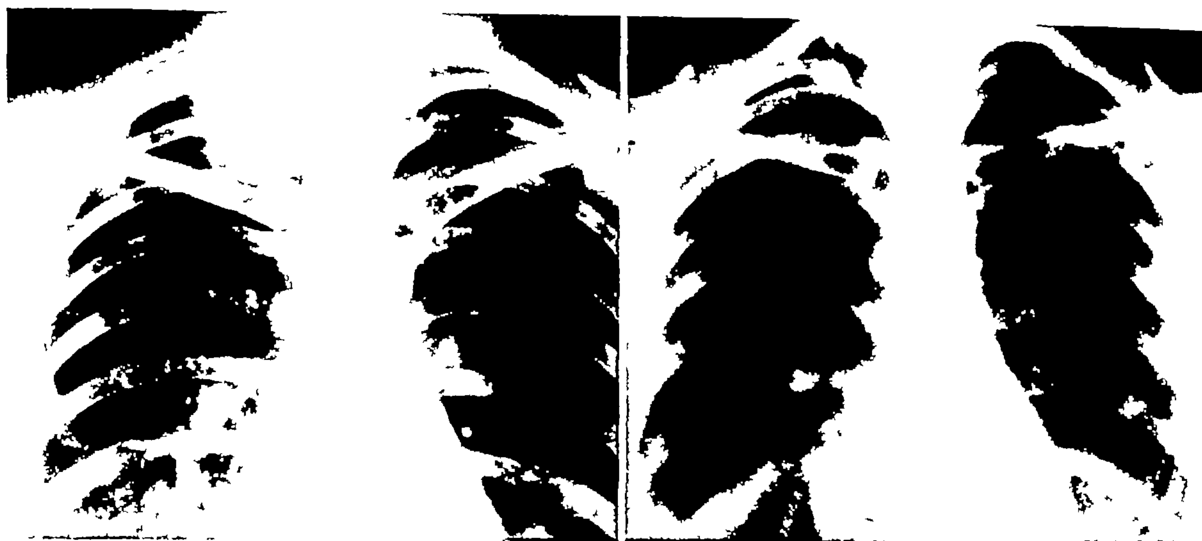


FIG 386 (*Left*) Roentgenogram showing a mediastinal (upper posterior) malignant neurilemmoma before surgical removal The mass was asymptomatic Exposure for the resection was through a right paravertebral incision over the first, second, third, and fourth ribs about one inch from the spinous processes The scapula was retracted laterally and the second and third ribs were resected, which permitted extrapleural resection of the malignant neurilemmoma (*Right*) Roentgenogram after removal of the tumor The patient is well 8 years after operation

ulated, grapelike masses of encapsulated semigelatinous tissue in addition to nodules of firmer, white granular tissue

In those malignant neurilemmomas originating in benign encapsulated neurilemmoma the tumors are said to be grossly encapsulated and on cut-section are usually firm in consistency with

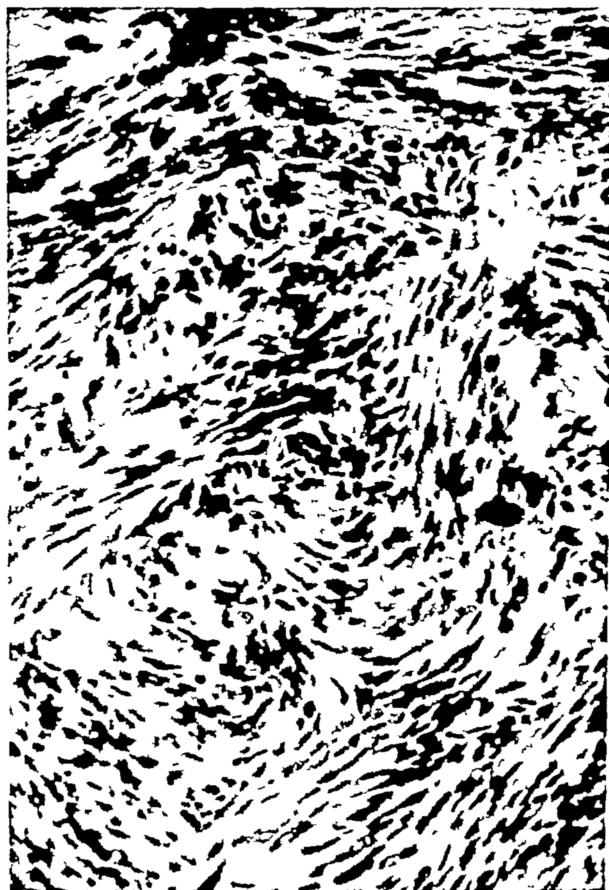


FIG 387 Malignant neurilemmoma, Grade I, originating in a plexiform neurilemmoma Treated by local excision Patient is living without evidence of recurrence 10 months after excision



FIG 388 Malignant neurilemmoma, Grade I, of right thigh, showing fine, palisaded, spindle-cell structure of the tumor The patient died in 21 months from lung metastases (Vieta and Pack, Am J Surg 82 116, 1951)

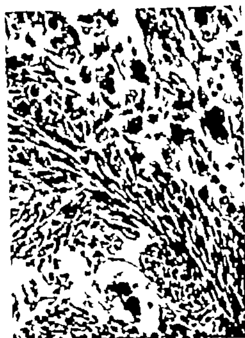


Fig. 389 Malignant neurilemmoma, Grade III, illustrating anastomosing spindle-cell strands intermixed with pleomorphic giant cells. (Vieta and Pack, Am. J Surg 82 416 1951)



Fig. 390 Anaplastic malignant neurilemmoma, Grade III (Vieta and Pack, Am. J Surg. 82 416 1951)

some areas being soft and jellylike and showing small cystic areas These ma lignant neurilemmomas in no way differ grossly from benign tumors and the diagnosis rests on histologic grounds and clinical behavior The authors have reviewed the neurilemmomas observed in their series and not one malignant neurilemmoma originating in an encapsulated neurilemmoma was found. Sev eral showed changes in histology from the usual architecture, which were at first thought to be in a transitional stage indicative of early malignant change, but each of the patients who had this type of tumor has remained free from local recurrence of the disease or metastasis despite only local excisions This



Fig. 391 Malignant neurilemmomas, examples of histologic variations of malignancy (*Left*) Highly pleomorphic spindle and giant-cell neurilemmoma originating in median nerve. (*Right*) Low-grade malignant change in plexiform neurilemmoma.

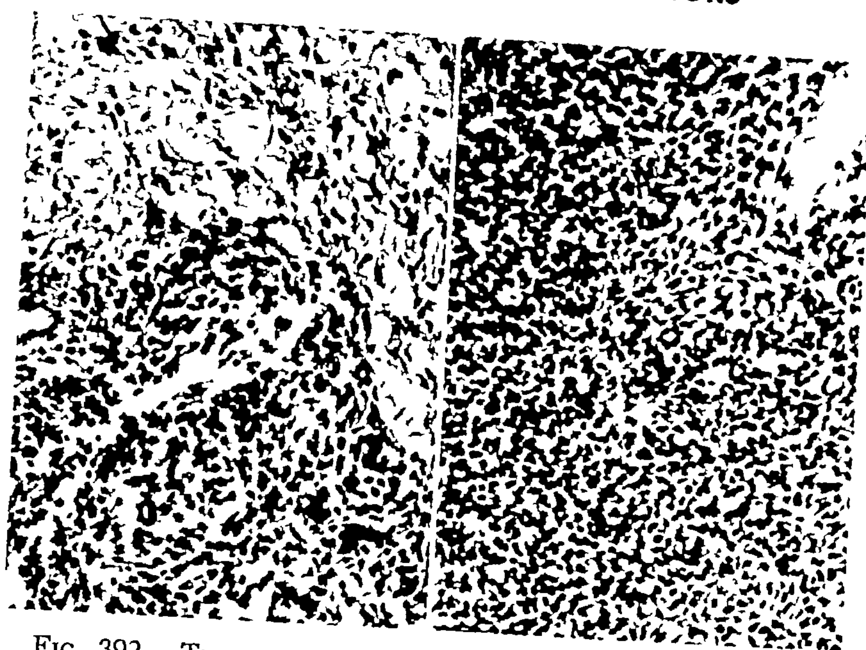


FIG 392 Two sections of a malignant neurilemmoma, Grade III, of right median nerve, illustrating structure, with Grade II spindle-cell regions to solid anaplastic Grade III regions

is not the usual history with malignant neurilemmomas The authors believe that a malignant neurilemmoma originating from a benign encapsulated neurilemmoma must indeed be a very rare tumor

These malignant tumors may by reason of contiguity produce pressure necrosis or osteitis of bone and occasionally invade and destroy the cortex of a neighboring bone The bone lesions of von Recklinghausen's neurofibromatosis can be found often by roentgenography

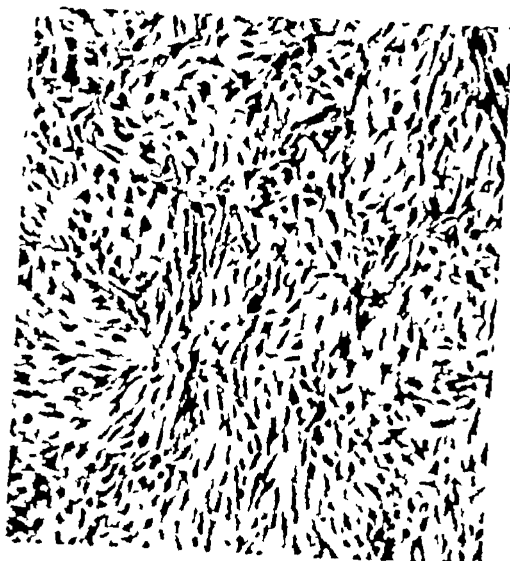


FIG 393 Malignant neurilemmoma, Grade III, of the cervical and brachial plexus, showing reticulated, edematous, spindle-cell and stellate-cell structure

The authors have never observed or seen reported an authenticated malignant transformation of neurofibroma or neurilemmoma in bone

The accompanying photomicrographs demonstrating various examples of these tumors adequately describe the micropathology without resorting to detailed word pictures that would confuse rather than clarify a varying histopathologic pattern

In those tumors which are classified as Grade I by the Broders method, the primary feature is usually that of a malignant neurilemmoma originating in a plexiform neurilemmoma. Large hyperchromatic nuclei interspersed with tissue showing a more benign appearance are often the earliest manifestation of the malignant transformation The reticular structure seen in these early malignant tumors is similar to that seen in the neurilemmoma showing the histologic structure usually denoted as the Antoni type B, reticulated, myxomatous form

Figure 388 represents a malignant neurilemmoma Grade I Although the malignant tumors with this type of architecture seldom metastasize, this tumor arising in the femoral nerve caused death by metastases

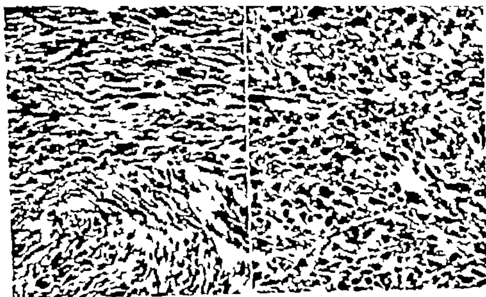


FIG. 394. Two sections of a malignant neurilemmoma, Grade III of sciatic nerve, showing mixed spindle-cell and giant-cell structure (Vieta and Pack, Am J Surg 82 416 1951)

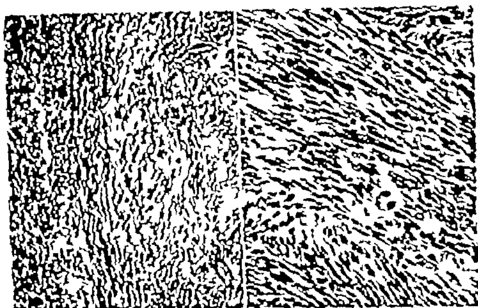


FIG. 395 Two sections of a malignant neurilemmoma Grade III of the common peroneal nerve, denoting first early malignant change in a plexiform neurilemmoma. Note the pleomorphic spindle-cell structure. (Vieta and Pack, Am. J Surg. 82.416 1951)

INICAL FEATURES OF ALIGNANT NEURILEMMOMA

There are no characteristic symptoms hich can be considered diagnostic. e *chief* reason the patient usually mes for advice is the presence of a mor mass In those patients with von ecklinghausen's disease the recent, ore rapid growth of a small mass hich may have been present without mptoms for a long time causes the pa tient to seek aid because of *the fear* of pain

The following symptoms occurring in our 31 patients sum up the clinical manifestations which first led the patient to seek medical aid growth of a painless mass, 23 *patients* growth of a mass with simultaneous pain, 3 patients pain present before any mass was *noted, 2 pa*tients paresthesias and hypesthesia before a *tumor mass was noted, 1* patient cough and dyspnea, 2 patients recur

rent or residual tumor on first examination at the hospital, 14 patients, and gross objective neurologic signs present when examined, 6 patients

Despite the fact that all these tumors arise in peripheral nerves, only 7 of the patients exhibited neurologic symptoms other than pain when examined This accentuates the observation that the nerve from which the tumor arises may appear to be inextricably bound within the tumor mass, yet there usually remain nerve fibers able to carry on some degree of function The lack of neurologic signs, therefore, does not signify that the tumors do not arise in peripheral nerves

The mean duration of symptoms was 49 months before a histologic diagnosis of a malignant tumor was made after the onset of symptoms.

The total duration from the onset of symptoms to death was ascertained in 14 patients and averaged 76 months The periods varied from 8 months to 21 years Seven of the entire group (31 patients) were clinically cured for more than 5 years after the last treatment

Malignant neurilemmoma is thus one of the more slowly growing cancers These tumors, however, like tumors in general, differ markedly in their clinical course Most remain localized for a long period, and death eventually occurs from massive local recurrence with ulceration, infection, pain, or hemorrhage, with resultant cachexia Metastases to the lungs may occur (7 of 14 patients who succumbed) as a fatal phenomenon

TREATMENT

Surgery

Successful treatment of the malignant tumors of peripheral nerves demands radical surgery at the earliest opportunity They must be treated either by radical local resection or amputation Each patient must be individualized One must consider therapy in the light of whether the procedure is for the extirpation of the primary neoplasm or for a recurrence, and whether the tumor is of a low- or high-grade malignancy where a primary radical local excision could not adequately eradicate the local malignant neoplasm.

By *radical local excision* is meant that the tumor plus its bed and any attached nerve, bone, muscle, or blood vessel must be excised en bloc Any "shelling" out of the neoplasm can but lead to a local recurrence Of necessity, the resulting operative defect must be through normal tissues on all surfaces The nerves of origin must be sectioned proximally and distally from the tumor Frozen section at the time of excision outside the region of intraneural spread of the neoplasm should be performed On the extremities, if a radical local excision does not meet all the requirements for excision through normal tissues, an amputation must be performed (Fig 57)

In the authors' experience, when local radical excision was the indicated procedure, restoration of nerve continuity has not been feasible Radicalness of the excision for prevention of local recurrence and cure is the prime surgical objective

The above plan of treatment is applicable mainly to that group of malignant nerve tumors appearing in the solitary form However, when at surgical exploration it is noted that in addition to the malignant tumor mass there are found nodular enlargements or tortuosity and thickness of branches of the involved nerve trunk or adjacent nerve trunks, even though a biopsy only reveals a plexiform neurilemmoma in these satellite foci, that limb should be radically sacrificed by amputation at the highest level, e g, interscapulothoracic amputation, hip-joint disarticulation, or hemipelvectomy (Fig 384) In the malignant neurilemmoma occurring in an extremity whose nerves are the site of

multiple plexiform neurilemmomas al though that malignant tumor may be removed by radical resection, the other nerves in the region have a tendency toward the same type of malignant transformation. This observation is especially noteworthy in the malignant neurilemmoma appearing on the basis of the multiple neurofibromatoses of von Recklinghausen Thus one has to deal later in these instances not with local recurrences but with multicentricity of origin in condemned segments of nerve tissue which may give rise to various histologic grades of malignant neurilemmoma It is for this important concept in pathologic interpretation that the most radical type of local excision or amputation is mandatory

The only exception is for the treatment of that smaller group of malignant nerve tumors classified as the Grade I malignant neurofibroma or neurilemmoma (myxoid neurinoma Geschickter) These grossly resemble the benign encapsulated neurilemmoma but are not completely encapsulated. Histologically there may be typical areas of palisading of the nuclei, the Antoni type A architecture, but for the most part the neoplasm is made of tissue of the reticulated structure designated as Antoni type B An occasional large hyperchromatic nucleus will be noted interspersed with this reticular pattern. This observation is often the earliest recognized manifestation of malignant neurilemmoma These changes have been noted for the most part in the plexiform neurilemmoma. The local excision in this rare group thus need not be as radical, but the nerve of origin must be excised. It may also be possible adequately to excise the neoplasm and restore continuity of the nerve of origin by nerve suture This fortuitous circumstance, however from a practical standpoint is rarely encountered, and few successes are reported.

In a number of isolated instances during the eradication of malignant nerve tumors and in order radically to excise the neoplasm through normal tissues on all sides the main blood vessels to an extremity may of necessity be sacrificed. The treatment heretofore has been amputation, not only because it constitutes a more radical removal of the nerve tumor but because of the probable loss of the limb due to interruption of its arterial blood supply with subsequent gangrene. Arteries may now be resected, and the defect corrected by vessel graft

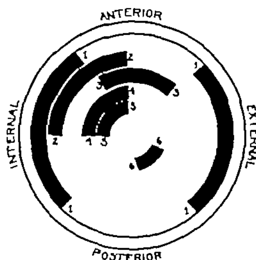


FIG. 396 Schematic cross-section of median nerve at the midarm level (from Kraus and Ingham) showing position of bundles as determined by electric stimulation of this level. 1 Pronator radii terest. 2. Flexor carpi radialis. 3. Palmaris longus. 4. Flexores digitorum. 5 Flexor pollicis. 6 Pronator quadratus (*Courtesy* E. C. Cutler and R. E Gross and Ann. Surg *104* 436 1936)

This procedure we believe, is indicated in Grades I and II tumors and should be limited to those *malignant* neurilemmomas occurring as solitary tumors and not be done when satellite nodules are noted along the branches of the parent nerve trunk, even though these satellites may be histologically benign.

Repair of Severed Nerves

Before division of a nerve that is to be repaired by end to-end suture tie-markers are placed in line on one surface above and below the tumor site so that the approximation may be accom-

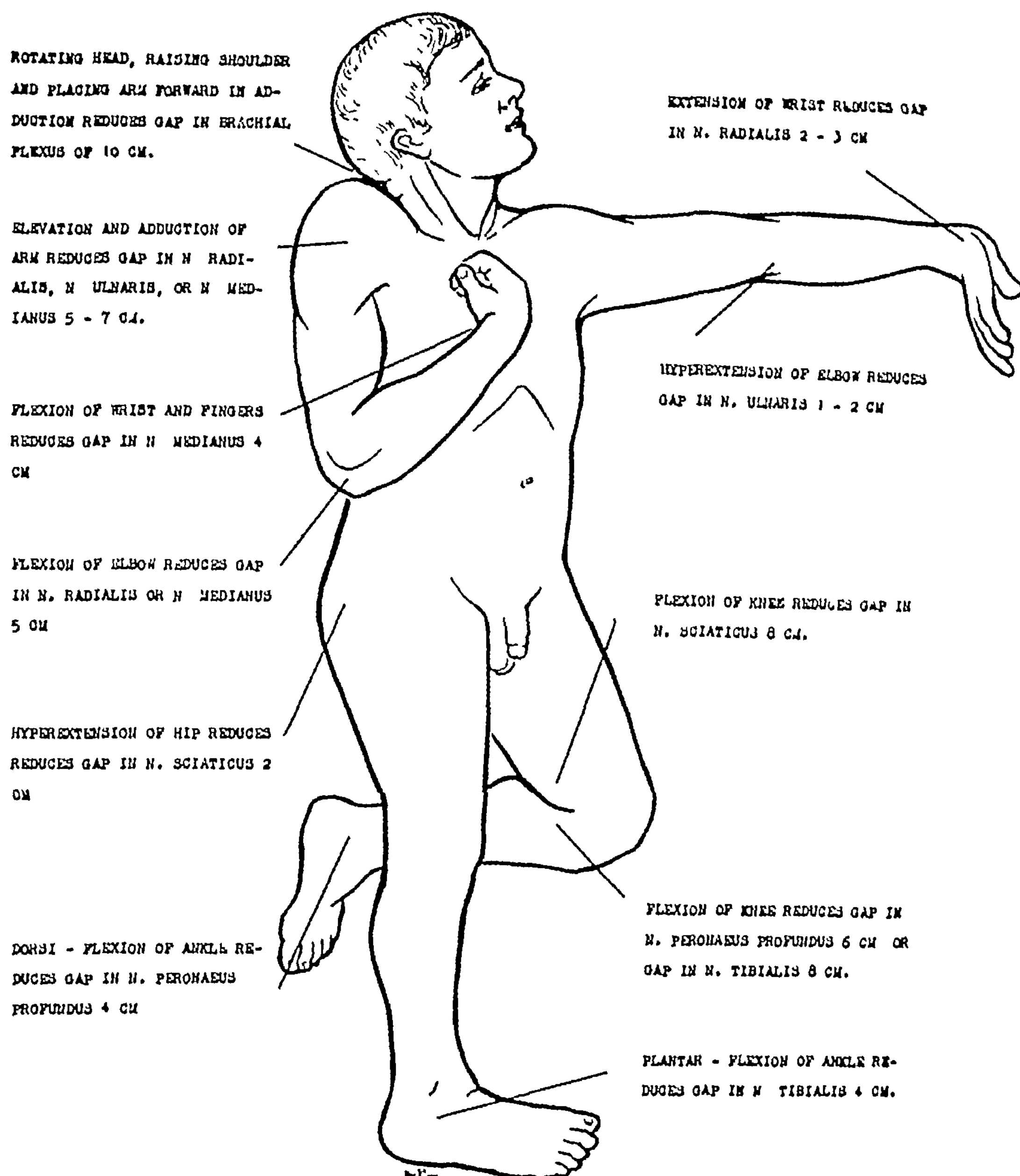


FIG 397 Diagrammatic representation of the amount of nerve defect which may be overcome by movement of joints as indicated (*After* Babcock)

plished without any rotation of the cut ends Fibers coursing to various muscle groups are distributed in a fairly definite pattern in the nerve trunk, and nerve bundles of the proximal end should be apposed to corresponding distal fascicles (Fig 396) Although perfect matching of the fascicular pattern may be an impossible goal, every effort should be made to obtain the best possible approximation of the nerve ends, for in this way the possibility of subsequent neuroma formation is reduced and that of nerve regeneration enhanced A clean division of the nerve at right angles to the long axis of the trunk is essential

If the gap between the cut ends of the nerve is relatively small, the natural slack and elasticity of the nerve may be sufficient to allow approximation. For a larger gap, positioning of the joints as shown in Figure 397 may allow approximation. However, the elbows and knees should not be flexed beyond a right angle, as subsequent straightening of the limb may inflict a traction injury on the nerve which may be even more serious than the primary division For a still larger gap, rerouting of the nerve, when this is feasible, may be necessary in addition to positioning of the joint The nerves best suited to this procedure

are the ulnar in the arm and forearm, where an additional 6 cm. can be gained, and the median in the forearm, where approximately 14.5 cm. can be gained. (Table 78.)

Very large gaps have been closed successfully by nerve grafts Homografts are uniformly successful. Seddon reported the results of nerve grafting in 58 cases In over one-half of the cases restoration of function by his criteria was as satisfactory as suture of the same nerve at the same level. However it is the opinion of most surgeons that autogenous nerve grafts should only be used when the nerve gap cannot be approximated by rerouting, proper positioning, or preliminary bulb suture.

Most surgeons prefer interrupted epineural sutures of 00000 silk or tantalum wire wedged on an atraumatic needle to approximate the nerve ends The latter suture material has some advantages in that the site of repair may be demonstrated by roentgenograms and any disruptions in the suture line noted. Young's or Tarlov's method of employing the plasma clot suture plus a silk or tantalum wire epineural suture to avoid tension would appear to offer a refinement in neurorrhaphy well worth following. Two sutures are placed, approximating the nerve ends on opposite sides of the nerve. These sutures are left long and snapped so that when the upper side of the nerve has been sutured, they may be used to rotate the nerve in order to suture the under side The sutures include 2 or 3 mm. of the nerve end and pass through the epineural coat only for this is the strongest portion of the nerve and provides the strongest suture line. The neurorrhaphy is but the first stage in rehabilitation. Adequate immobilization with removable splints is preferred to the use of plaster encasements on the extremities

However satisfactory any nerve repair and regeneration might be, an extremity would be functionally useless if the denervated muscles are permitted to undergo fibrosis or the joints to become ankylosed. Gradual extension of a flexed joint can begin after 20–30 days and be completed in 6 weeks time. Physical therapy must be employed after neurorrhapy Galvanic stimulation daily helps to prevent atrophy and fibrosis Windows cut in casts over paralyzed muscle bellies allow electric stimulation of the denervated muscles 2 or 3 days after nerve suture. Active and passive motion of the small joints must be stressed along with other physiotherapeutic methods of massage, use of heat, and proper splinting The effector mecha

TABLE 78 MAXIMUM GAPS IN PERIPHERAL NERVES IN WHICH END-TO-END SUTURE IS POSSIBLE*

	By Slack and Elasticity (cm.)	*By Joint Position* (cm.)	*By Re-routing* (cm.)	*Totals* (cm.)
Brachial plexus	1.5	3–7		11.5
Radial in arm	3.0	5–7		15.0
Radial in forearm	1.5	4–5		10.5
Ulnar in arm	3.0	7	6.0	16.0
Ulnar in forearm	1.5	5	6.0	12.5
Median in arm	3.0	5–7		15.0
Median in forearm	1.5	3–4	14.5	23.0
Sciatic	3.0	3–8		14.0

* After Babcock.

nism must be preserved until nerve regeneration has taken place

Physiotherapy carried out by technicians is but a small part of the process of rehabilitation The patient himself must be taught to perform his own passive movements through a full range of motion and apply massage many times during the day to prevent fibrosis of joints and the appearance of abnormal pain patterns

Radiation Therapy

Peripheral nerve tumors, both benign and malignant, are notoriously radioresistant neoplasms Only in an exceptional case is an appreciable diminution in the size of a malignant neurilemmoma noted when radiation therapy has been delivered Although infrequently radiation therapy may cause shrinkage of the tumor, this result is obtained mainly through the effect of therapy on the anatomic structures of the tumor bed and not through its direct effect on the tumor

In some cases treated by radical local excision, postoperative radiation therapy was administered with the idea of preventing local recurrence of the neoplasm Although none of the patients so treated by combined surgical and radiologic technics developed a local recurrence during the period of observation, neither have a larger group treated only by surgery developed a local recurrence We know of no malignant neurilemmomas that have been cured by radiation therapy, and its use for palliation is equivocal Surgical resection offers the only hope for eradicating the various types of malignant nerve tumors

RESULTS OF TREATMENT

The authors' series of 31 patients bearing malignant neurilemmomas of different degrees of malignancy and treated by various methods will be analyzed to discern which technics are best suited to treat successfully this group of neoplasms It becomes apparent that certain surgical principles must be rigidly adhered to in order to better the end results of treatment

Twenty patients of the series had been previously treated or observed for varying periods before coming to this clinic Of these patients 14 had prior surgical treatment Thirteen of these 14 had residual or recurrent neoplasm in the operative regions when first seen here, thus denoting probable inadequate surgical procedures at the former operative attempts Of the 14 patients previously treated by some type of local excision, 8 had one prior excision, 1 had two operations, 4 had three attempts, and 1 had four procedures The primary treatment proved to be adequate and required no further surgery in only 1 of the 14 patients Even this patient, however, had three operations at another hospital before the neoplasm was controlled

In 6 of the 20 patients previously treated when a diagnosis of malignant soft part tumor had been correctly made, the therapy given was exclusively x-ray therapy or radium In 4 of the patients, x-ray therapy was given before any definite histologic diagnosis was established Irradiation is known to be ineffective

The treatment rendered here to the 20 previously treated patients plus the 11 without prior definitive treatment is tabulated in Table 79

The question arises as to what effect irradiation has upon these tumors From our data, including those who had received radiation therapy before admission, plus those treated postoperatively or for palliation, we have noted that of the 19 treated exclusively by some form of radiation therapy only 2 tumors showed appreciable diminution in size Not infrequently malignant neurilem-

TABLE 79 TYPES OF TREATMENT OF MALIGNANT NEURILEMMOMA

(Authors Series)

Type of Treatment	Number of Cases
Total cases	31
Radical local excision	12
Radical local excision after preoperative x ray therapy	1
Radical local excision plus postoperative x ray therapy	2
Postoperative x ray therapy plus amputation	5
Primary amputation	4
Amputation after other forms of treatment have failed	1
Postoperative x ray therapy after local excision elsewhere	1
Palliative x ray therapy	3
Palliative amputation or excision	2

moma recurs after long intervals of inactivity in an irradiated region. This time interval may be similar in period to the time of recurrence after surgical removal It appears from these observations that radiation therapy does not destroy the tendency toward development of a new tumor or prevent recurrence of the original one present. Therefore, from these data little can be expected from preoperative or palliative x ray therapy and postoperative x ray therapy should not be expected to keep the disease under control if it has not been completely eradicated by surgical measures

It is interesting to note the end results of a radical surgical approach and the causes of failure Twenty seven of our patients were treated surgically 15 by radical local excision, and 10 by amputation.

The results of treatment are given in Table 80 Thirty-one cases are available for analysis The neoplasms in five cases were inoperable when first examined, although one patient had an exploratory thoracotomy and another was subjected to a palliative hip-joint disarticulation for an infected, bleeding thigh tumor

Seventeen patients with malignant



FIG. 398. Malignant neurilemmoma of right radial nerve. Local excision. The patient is living 8 years after excision without evidence of recurrence (Vieta and Pack, Am. J. Surg 82:410, 1951.)

neurilemmoma were treated by radical local excision, 16 by the authors and 1 elsewhere but followed up here In reviewing the cases treated by radical local excision in which recurrence occurred and caused death, both tumors situated in the neck recurred locally, which precluded any further surgical treatment The tumor in one patient was located in the upper extremity and recurred locally, an amputation was then performed This patient has survived six years after that procedure (Table 80)

Those patients treated by amputation followed by local recurrence in the stump present some features of interest. One patient had a local recurrence 23 months later in the stump of an amputation through the upper third of an arm He refused interscapulothoracic amputation for 17 months This latter operation was followed with another recurrence in the operative site after 13 months This slowly growing tumor did not cause death until 33 months later It is possible that earlier amputation at the shoulder girdle would have controlled this sarcoma One patient with local recurrence in a stump through the surgical neck of the humerus probably would not have benefited by further surgery which was advocated but refused Another patient had recurrence in the abdominal wall within 19 months after a hemipelvectomy, the patient died 3 months later The line of section of the lumbosacral nerve trunks was near the upper limits of the tumor despite the most radical type of surgery possible

From our material it would appear that results from local excision (4 of 17 lived 5 or more years, 5 other patients,





Fig 399 Malignant melanoma associated with von Recklinghausen's neurofibromatosis (*Left*) Bathing-trunk nevus in which a melanoma developed which metastasized to the axillary nodes and brain Note numerous cutaneous fibromas scattered throughout (*Right*) Turban tumor (bull-dog scalp) A malignant melanoma developed in this lesion and metastasized to the cervical lymph nodes

TABLE 80 END RESULTS OF SURGICAL TREATMENT OF MALIGNANT NEURILEMMOMA

(Authors Series)

A Results of Radical Local Excision (Seventeen Cases)	
Local recurrence	3
No local recurrence	13
Recurrence after local excision here followed with amputation	1
End results	10
Lost to follow up	5
Living with no recurrence	8
Died with no evidence of local recurrence	1
Died with local recurrence (nine months 15 months)	2
Lived five years or more without evidence of disease	4
B End Results of Treatment by Major Amputation (Eleven Cases)	
Palliative amputation	1
Recurrence in amputation stump	3
Died in more than five years with lung metastases and no evidence of local recurrence (eleven years)	1
Died in less than five years with local recurrence and/or lung metastases	7
Lived five years or more without evidence of malignant tumor	3

when lost to follow up had lived on an average of 25 months 4 other patients still under follow up observation are living an average of 26 months) are better than those following amputation, in which only 3 of 11 lived 5 years or more without recurrence. In the 11 instances of amputation however 7 represent failures from previous local radical excisions In the group of 4 amputees not previously treated by radical local excision there was not a single patient who lived 5 years or longer without recurrence However each had a large, bulky rapidly growing tumor 2 in an upper and 2 in a lower extremity On the other hand 3 patients were saved by amputation when local radical excision had previously failed another lived 10 years before succumbing to metastases from the malignant neurilemmoma (Table 81)

Table 82 summarizes the end results by all types of treatment

TABLE 81 FIVE YEAR SURVIVALS AS DETERMINED BY OPERABILITY STATUS OF MALIGNANT NEURILEMMOMA

(Authors Series)

Recurrent operable	5 cases
Primary operable	1 case
Surgery elsewhere	1 case

TABLE 82 FIVE YEAR END RESULTS IN THE TREATMENT OF MALIGNANT NEURILEMMOMA

(Authors Series)

Total number of cases		31
Indeterminate group		
Total number of indeterminate results		11
Dead as a result of other causes and without recurrence	1	
Lost track of without recurrence	5	
Patients followed up less than five years and still under observation	4	
Lost track of without recurrence over five years	1	
Determinate group		
Total number minus those of indeterminate group		20
Failures		
Total number of failures		14
Dead as a result of tumor	13	
Lost track of with cancer (probably dead)	1	
Living with recurrence	0	
Successful results		
Free from cancer after five years or more		6
Net five-year end results		
Successful results divided by determinate group 6/20		30 per cent

The end result is 30 per cent "clinical five-year cures"

If the data are analyzed for factors other than the type of therapy used, it



FIG 400 Neurofibromatosis with associated malignant neurilemmomas in siblings (*Left*) *Roentgenogram illustrating a huge malignant neurilemmoma involving the upper right arm* (*Right*) Roentgenogram of a sister of the patient on the left who suffered from a posterior mediastinal neurilemmoma This patient also had malignant neurilemmomas of both thighs which had produced pulmonary metastases (Her clinical course is discussed in case report No 69)

at once comes to mind whether the histologic type and grading of the tumor influence the end results (Table 83). Classifying the tumors in the seven patients who died as a result of the neoplasm, these tumors were graded according to the Broders classification into Grades I, II, III, and IV

TABLE 83 END RESULTS IN RELATION TO THE GRADING OF MALIGNANT NEURILEMMOMA

(Authors' Series)

End Results	*Total Cases*	*Grading of Tumor* I	II	III	IV
Patients dying of uncontrolled malignant neurilemmoma	13	2	7	4	0
Patients living five or more years without recurrence	7	2	4	1	0

All seven patients who died with lung metastases while under observation had been subjected to amputation Three had primary amputations, while the other four were subjected to amputation for recurrent or residual neoplasm Two of these seven, in addition to lung metastases, developed local recurrence in the amputation stump The histologic grading of these seven tumors were three cases, Grade II, three cases, Grade III, and one case, Grade I

In one patient the malignant neurilemmona was classified as only Grade I, yet the patient died of pulmonary metastasis, this was an unexpected result as the majority of such tumors with similar histologic pattern may recur locally many times and the tumor become increasingly anaplastic in structure before metastases occur These fatal blood-borne metastases appear to be related to the incidence of local recurrence and to the histologic grading of the tumor Warren has pointed out that patients with neurogenic fibrosarcoma exhibiting tumor giant cells survive a definitely shorter period than those without giant cells

In this material there were fifteen patients who had locally residual tumors after prior treatment or recurrence in the operative site following excision Thus it is obvious that the primary local

excision or amputation is often inadequately radical. Recurrence offers a grave prognosis, not only regarding the likelihood of metastases but also with regard to a fatal issue from the neoplasm. Hence, adequate primary removal is of first importance as it is readily apparent in reviewing this material that persistence of the tumor shows a *tendency to greater anaplasia* in the succeeding recurrences, thus giving a setting for fatal metastases from the more rapidly growing, more highly anaplastic growths

From Table 83 it appears certain that the end results are definitely related to the anaplasia of the tumor

The *relationship of neurofibromatosis* to malignant neurilemmoma as it affects the end results is summarized in Table 84.

TABLE 84 RELATIONSHIP OF NEUROFIBROMATOSIS TO END RESULTS IN MALIGNANT NEURILEMMOMA

(Authors Series)

	Number	*Per cent*
Patients dying with uncontrolled malignant neurilemmoma		
Associated with neurofibromatosis	4	30
Unassociated with neurofibromatosis	9	70
Patients living five years or more without recurrence		
Associated with neurofibromatosis	4	57
Unassociated with neurofibromatosis	3	43

It has often been stated that patients with malignant neurilemmoma occurring on the basis of von Recklinghausen's neurofibromatosis are infrequently cured. These data though based on a small series of thirty-one cases do not agree with this statement. Among the seven patients with clinical cures three had no stigmas of this disease, two had frank general neurofibromatosis and two others had the abortive or forme fruste type. Among the thirteen patients dying with uncontrolled malignant neurilemmoma, four had unquestioned neurofibromatosis and nine had no stigmas of the condition described in their clinical records.

It has been the authors experience that those tumors arising in major nerve trunks are clinically the more malignant. Only two patients with clinical five-year cures had their tumors originating in major nerves both having cancers of the median nerve. The other five arrested cases had tumors which were relatively superficial and had their origin in plexiform neurilemmomas

Of the thirteen patients dying from this neoplasm, nine of the tumors originated in named nerves or plexuses In three the process was so extensive that *in even these, though appearing to arise* on the basis of large plexiform neurilemmomas the malignant tumors could have originated in the major nerves of the area, *e g.*, cervical plexus and mediastinal nerves

CASE REPORT NO 68 MALIGNANT NEURILEMMOMA OF HAND AND ARM

D D a 24-year-old Italian American man, applied on April 1 1930 complaining of a swelling of the left forearm and left hand. One year before admission he had been operated on for a tumor of the left forearm and a smaller tumor on the dorsum of the left hand. These tumors rapidly recurred, and at the time of his initial examination they were of their original maximal size

When he was first seen, he was unable to extend his hand, due to marked deformity and crossing of his fingers. The motion of the left hand was practically gone. There was a diffuse soft, smooth and tender

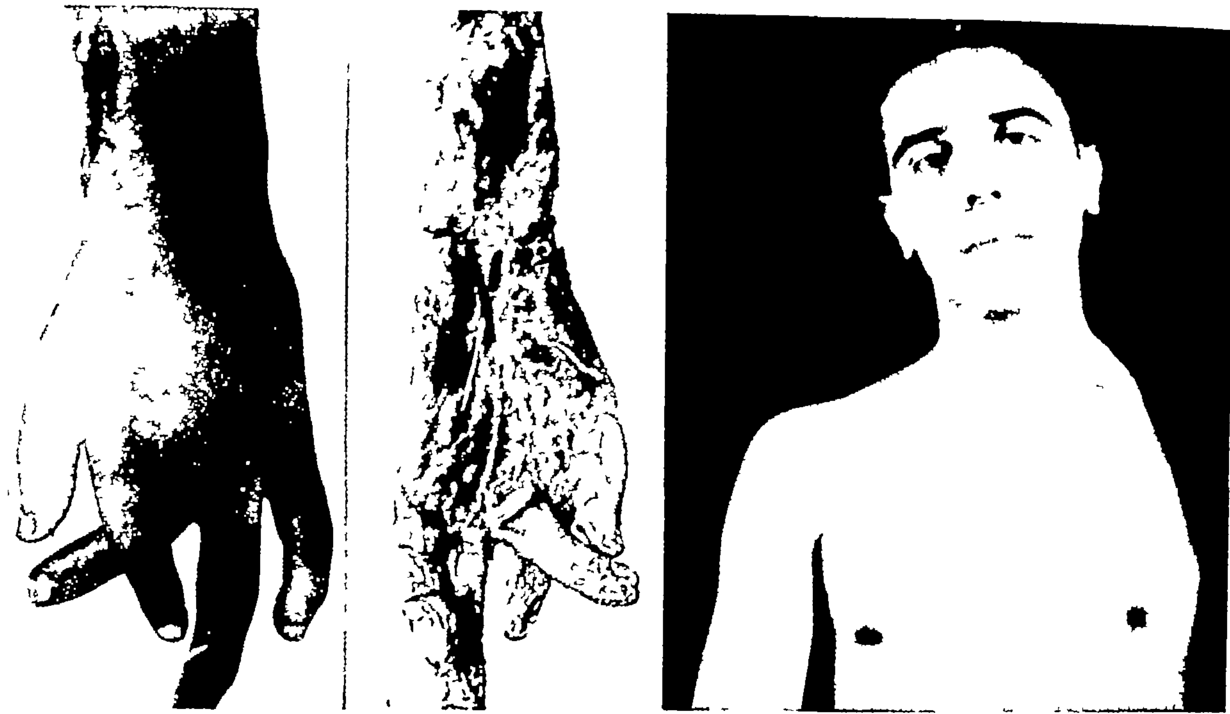


FIG 401 Malignant neurilemmoma of the hand treated by interscapulothoracic amputation (*Left*) Amputated specimen showing the malignant neurilemmoma Note congenital locked fingers (*Middle*) Dissected specimen illustrating extent of the malignant neurilemmoma and congenital locked fingers (*Right*) Postoperative photograph subsequent to interscapulothoracic amputation which was necessitated by repeated proximal recurrences, the last of which was in the base of the neck Patient living and well 20 years after last operation (Case report No 68)

swelling on the radial side of the left forearm, involving the dorsum and body of the left hand The original tumor was analyzed and proved to be a malignant neurilemmoma, Grade I In May, 1930, an attempt was made at local removal of these two masses, but the tumor was so deeply infiltrating between the bones of the hand that an amputation of the left forearm through the upper end of the radius and ulna was done The tumor was a malignant neurilemmoma, Grade I Examination of the specimen showed several tumors of the same type not definitely connected One was a fusiform tumor, 9 × 4 × 3 cm in diameter, along the medial aspect of the radius, another fusiform tumor, 4½ × 2 cm, was situated on the dorsal surface of the border between the radius and the ulna, and another tumor, 7 × 3½ cm in diameter, was on the ventral surface of the forearm between the radius and ulna Between the first and second and the second and third metacarpal bones, there were several soft, pink tumor masses each ranging about 1½ × 2½ cm in diameter A branch of the median nerve to the lateral second and medial first fingers showed a small fusiform swelling This last nodule was a neurofibroma, the other tumors were malignant neurilemmomas, Grade I

In November, 1933, another mass, 8 × 5 cm in diameter, was felt in the cubital space The right median nerve was also palpated and appeared to be nodular On November 22, 1933, a radical surgical excision of the recurrent tumor was performed, and one lymph node in the extreme outer aspect of the left axilla was excised The specimens revealed malignant neurilemmoma, Grade I, metastatic to one axillary node Because of the proved tendency of the tumor to recur, a more radical operation was planned

On December 6, 1933, a midhumeral amputation of the left stump and an axillary dissection in continuity with the medial aspect of the left upper arm was performed Dissection of the median nerve in the distal 7 cm revealed a progressive enlargement of the nerve trunk until in the most peripheral portion the nerve was 7 × 9 mm in size and on section revealed regions of pinkish-white, translucent tissue of firm consistency The ulnar nerve showed similar but less developed tumefaction and purely white neuromas in the distal portion The axillary tissue showed most of the nodes

to be replaced by malignant neurilemmoma, Grade I The nodules on the nerves were benign neuromas

Six months later in May 1934 there was a definite recurrence of the tumor in the stump it measured 4 × 6 cm in diameter An elliptical incision was made over the amputation stump and the tumor was excised, together with a portion of the short head of the biceps and posterior portion of the medial head of the triceps. Again this tumor was a malignant neurilemmoma

A very small nodule was discovered in the region of the left subscapular muscle Because of this continued recurrence, the patient was admitted for a left interscapulothoracic amputation which was performed on February 25 1935 The specimen showed that the trunks of the brachial plexus were solidly involved by tumor tissue so that the individual branches or trunks of the plexus could not be separated The specimen proved to be a malignant neurilemmoma, still Grade I Four months following the operation the patient had gained 20 lbs in weight.

On December 19 1935 an indefinite swelling appeared beneath the central part of the scar of the interscapulothoracic amputation. This was a fixed tumor mass, nonulcerated, measuring 5 × 6 cm in diameter which appeared to extend intercostally Under general anesthesia this mass was surgically dissected free and at the time of exposure the base of the wound was treated by the interstitial deposition of 11 gold seeds containing 15 77 mc. of radon. After the wound had healed, postoperative x-ray therapy was given with the following factors 1 single portal over the scar 200 kv 0 5 mm of copper 50 cm target skin distance, 30 ma. size of portal 13 × 18 cm., and 200 r daily for a total dose of 3000 r units. The last excised specimen also revealed malignant neurilemmoma, Grade I

Comment

There are several interesting and unusual features illustrated in this case (1) the tendency of malignant tumors involving the peripheral nerve sheaths to extend in a centripetal manner in this instance from the hand to the neck, and in each instance recurring after radical dissections and radical amputations which, according to the account of the pathologist, were well beyond the limits of the tumor (2) the unusual phenomenon of the malignant neurilemmoma maintaining *its low grade of malignancy* although repeatedly recurrent (3) ultimate success for a 20-year cure through perseverence and optimism on the part of the patient and the surgeon.

CASE REPORT NO 69: MULTIPLE MALIGNANT NEURILEMMOMAS IN A PATIENT WITH NEUROFIBROMATOSIS

R. N was a 12-year-old Italian American girl who since birth had shown the cutaneous stigmas of von Recklinghausen's disease of peripheral nerves, with circumoral pallor and numerous café-au lait spots over the trunk, chest, and arms Her sister had previously been treated for a malignant neurilemmoma There were innumerable subcutaneous nodules with moniliform bead

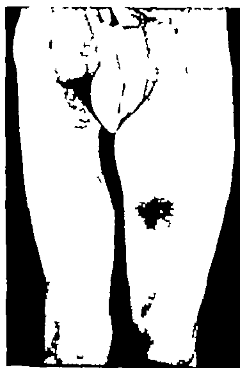


FIG. 402. Von Recklinghausen's neurofibromatosis. The patient has a recurrent malignant neurilemmoma of the anterior aspect of the left thigh which produced pulmonary metastases. Another tumor of similar type had been excised from her right thigh. (Case report No. 69) Her sister died of malignant neurilemmoma.

ing of the nerve trunks, particularly in the cervical regions For eight months she had been aware of a gradually enlarging tumor involving the anterior surface of the left thigh This encapsulated lesion was surgically excised, it was a malignant neurilemmoma of low-grade malignancy Two years later a series of two rapidly growing subcutaneous masses appeared in the right leg, one in the medial aspect and the other superior to it toward the groin On excision the lower mass was a malignant neurilemmoma of a cellular type, Grade III, capable of metastasis The superior nodule was a plexiform neurilemmoma One year later a rather large tumor, 4 or 5 cm in diameter, situated in the right arm above the cubitus, was surgically removed It was a plexiform neurilemmoma with multiple myxomatous nodular lesions extending along the nerve trunk A few months later a second mass appeared in the left thigh superior to the scar of the former excision This grew to enormous extent because the patient refused operation Later a radical surgical excision was performed for a second neuromyxosarcoma of the left thigh The right ankle showed the characteristic elephantiasis neuromatosa, one of the pathognomonic features of von Recklinghausen's disease of peripheral nerves The patient died three years later of generalized sarcomatosis and pulmonary metastasis This case represents the occurrence of multiple malignant neurilemmomas in a patient with von Recklinghausen's disease (Figs 400 and 402)

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TUMORS OF THE SYMPATHETIC GANGLIA

The sympathetic ganglia and the paraganglionic tissue give rise to an interesting group of tumors of the peripheral nervous system One of these, the neuroblastoma, is one of the most frequent and fatal tumors of childhood, and another, the pheochromocytoma, arising usually from the medulla of the adrenal gland, presents the clinical picture of hyperadrenalism by which the diagnosis can be made and which must be carefully controlled during the operative removal

The tumors of the sympathetic ganglia are

Benign
- Differentiated ganglioneuroma

Malignant
- A Partially differentiated ganglioneuromas
- B Neuroblastoma (sympathicoblastoma)

Tumors of the paraganglionic cells are

- Paraganglioma (benign and malignant)
- Pheochromocytoma (benign and malignant)

Tables 76 and 77 show the development of the various cell forms of the sympathetic nervous system and the neoplasms arising from each

GANGLIONEUROMA

Ganglioneuromas have their origin in the sympathetic ganglia or from cells of their anlage and consequently are most often found along the path of the sympathetic chain from the base of the skull to the pelvis, as well as in the adrenal medulla They may also arise within the central nervous system They are characterized frequently by the large size they may attain

LOCATION

The most frequent location of ganglioneuromas *is the posterior mediastinum,* rarely in the anterior mediastinum Of the 243 neurogenic tumors reported by Stout (1947), 63 were intrathoracic Rogers and Keogh (1950) reviewed 90 intrathoracic ganglioneuromas reported in the literature to that date

The tumors in the posterior mediastinum, as well as those in retroperitoneal locations, may invade the spinal canal, producing the so-called hourglass tumor, discussed previously under neurilemmomas

They may arise in the cervical region, although their occurrence here is quite rare (13 reported cases up to 1939 Shumaker and Lawrence) They may arise from the nodose ganglion of the vagus nerve Only 3 such cases have been recorded in the literature. One such patient bearing a malignant ganglioneuroma, treated by the authors, is presented in detail in case report No 70

Those encountered in the abdominal cavity are usually retroperitoneal In Stout's series of 243 tumors, 134 were abdominal in origin, 14 were in the lumbar region, and 31 in the adrenal glands Multiple tumors may occur similar to

the multiple neurofibromas in von Recklinghausen's disease and may at times be very numerous.

They have been reported occasionally to occur in strange anatomic regions such as the tongue, spermatic cord, stomach breast, uterus vulva, kidney and knee joint, arising from embryonic anlagen which have migrated.

AGE AND SEX

Despite the fact that about 75 per cent of these tumors appear before the age of 20 they are relatively rare in very young children. In Stout's series of 243 neurogenic tumors, 60 per cent were in patients below 20 years of age. Females predominated in a ratio of 3 to 2. Patients with cervical sympathetic ganglioneuromas range in age from 2½ to 36 years—70 per cent occurring in children—with an equal sex distribution. Heuer and Andrus (1940) found 74 per cent of patients with intrathoracic ganglioneuromas to be under 10 years of age.

PATHOLOGIC CHARACTERISTICS

Ganglioneuromas usually present a smooth ovoid appearance. They appear well encapsulated and are usually separated with ease from the contiguous structures They are discrete and may be lobulated or dumbbell in shape The outer portion is usually yellowish white in color and firm in consistency whereas the inner portion may show hemorrhage and necrosis. Microscopically ganglioneuroma is composed of differentiated ganglion cells surrounded by a neurofibromatous stroma containing many neurites sheathed by Schwann cells When grown in vitro these tumors reproduce themselves beautifully The tumors vary microscopically from those which are completely differentiated to others designated by Stout as partially differentiated ganglioneuromas In about 25 per cent of all ganglioneuromas some degree of anaplasia is noted. The entire tumor may show an admixture of cells varying from complete differentiation through all stages of undifferentiation to some which are completely anaplastic. Stout states that 18 per cent of these tumors metastasize. In another group one portion of the tumor will be completely differentiated, whereas another portion of the same tumor will reveal all the characteristics of a malignant neuroblastoma. Sixty five per cent of this group produce metastases.

Malignant neuroblastomas sometimes revert to benign ganglioneuromas (either spontaneously or as a result of radiation therapy)

SYMPTOMS AND DIAGNOSIS

These tumors compress and distort rather than infiltrate the neighboring structures. They usually grow slowly producing no symptoms except an asymptomatic mass in an accessible region or an unexplained shadow roentgenographically seen in an inaccessible location (posterior mediastinum abdomen) They sometimes grow to large size and have been described as weighing 6 kg. The symptoms are due to the effects of pressure upon contiguous structures Those in the neck arise either from the cervical sympathetics or more rarely from the nodose ganglion of the vagus nerve. (See case report No 70) Those arising from the cervical sympathetic ganglia usually produce a Horner's syndrome No specific symptoms are produced by direct vagal pressure, as a rule, by those tumors arising in the nodose ganglion When the tumors increase in size, pressure against the trachea may produce persistent cough dyspnea, stridor and cyanosis Pressure on the laryngeal nerves may alter the quality of the voice These tumors arise from paravertebral structures and pro-

duce a rather characteristic sign, namely, the anterolateral displacement of the carotid artery A triad of symptoms, which consists of (1) a tumor, usually fixed in the depths of the neck, (2) an anterolaterally displaced carotid artery, and (3) freely movable skin which overrides the tumor, is highly suggestive of a neurogenic tumor, usually a ganglioneuroma

It is seldom possible to make a preoperative diagnosis without a biopsy, although the nature of the growth may be suspected from the age of the patient, its anatomic position, its insidious growth, paucity of symptoms, and its roentgenographic appearance

Roentgenographic Appearance

X-rays of the chest may show a well-circumscribed mass, most often in the posterior mediastinum The adjacent ribs and vertebra may or may not show thinning or erosion When the ganglioneuroma is of the so-called dumbbell or hourglass variety, x-rays may show a paravertebral mass and erosion of the pedicles and enlargement of the intervertebral foramen Gray, Shepard, and Dockerty divide the mediastinal space into three compartments and state that the anterior compartment is the anatomic region in which dermoid cysts and thymomas tend to arise, the middle compartment is the site of bronchogenic carcinoma and lymphosarcoma, and the posterior compartment is the site of the origin of the lymphosarcoma and neoplasms of neurogenic origin—including the ganglioneuromas An artificially induced pneumothorax may prove the extrapleural position of the tumor

TREATMENT

The treatment of ganglioneuroma is surgical extirpation These tumors are radio-resistant, and radiation therapy is not indicated for their control They are well encapsulated and separate with remarkable ease from their beds, in the usual case In the neck, meticulous dissection must be accomplished to separate the tumor from the various structures of this anatomic location An incision along the anterior sternocleidomastoid muscle with transection of the sternocleidomastoid muscle will afford good exposure If the tumor arises from the sympathetic ganglia, these may be resected with the tumor even though a Horner's syndrome develops In those tumors arising in the nodose ganglion of the vagus, the neoplasm may be dissected

The prognosis for benign differentiated ganglioneuromas is excellent Theoretically, in a slowly growing ganglioneuroma, if surgical resection is fraught with hazardous technical problems with possible damage to normal structures, these tumors would best be left alone However, since 25 per cent of them present segments of undifferentiation and because there is no way of knowing which tumor is completely differentiated and which is not, it is urged that every attempt be made to extirpate all such tumors

The excision of a mediastinal tumor may be difficult because of large blood vessels running over or through the tumor, which may be firmly adherent to vertebrae or ribs The intercostal incision is usually employed

The technical considerations of resection of intrathoracic tumors of peripheral nervous structures are presented in Chapters 26 to 29

Partially Differentiated Ganglioneuromas

As mentioned previously, in Stout's extensive study of ganglioneuromas, he observed that malignant transformation was occurring in 25 per cent of the encapsulated benign ganglioneuromas Because of this feature it is essential to resect completely all benign ganglioneu-

romas Pool *et al* have partially resected intrathoracic ganglioneuromas because of technical difficulties Data are not available concerning the incidence of malignant changes in so-called benign intrathoracic ganglioneuromas and only further observation of their patients and increased histologic data pertaining to this feature will either justify or condemn their practice of partial resection.

The high incidence of metastases produced by partially differentiated ganglioneuromas emphasizes their malignant character and stresses the radicalness of attempts at surgical ablation. If histologic examination of an apparently benign ganglioneuroma reveals evidence of malignant changes, the treatment should be the same as for neuroblastoma —radical surgical resection followed by postoperative irradiation.

In Taylor and Ackerman's series of intrathoracic tumors they observed seven partially differentiated ganglioneuromas Three of these patients are living, but only one is free of metastases longer than five years It is of interest that most of these neoplasms occurred in children.

An interesting tumor described by Mullan supposedly arising from a thoracic ganglion presented features of a benign ganglioneuroma with melanin within its cystoplasm in certain sections while other parts of the same tumor revealed nonpigmented neuroblastomatous features The metastases consisted of the same dual cellular elements

GANGLIONEUROMA CASE REPORTS

The following case report presents the clinical features and mode of attack of a malignant (partially differentiated) ganglioneuroma of the nodose ganglion of the vagus nerve.

CASE REPORT NO 70: MALIGNANT GANGLIONEUROMA OF THE GANGLION NODOSUM OF THE VAGUS NERVE

The patient, an 11½-month-old white female suffered from a mass on the right side

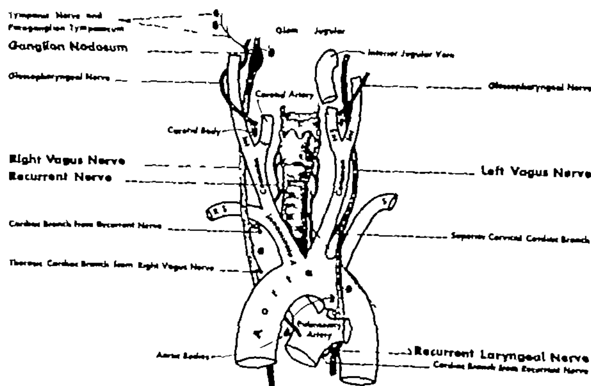


FIG. 403. Anatomy of the vagus nerve showing the nodose ganglion. The various ganglia and the paraganglionic structures of the parasympathetic nervous system are presented to show the sites of origin of ganglioneuromas and paragangliomas in the cervical region. (Pack, Ariel, and Miller A.M.A. Arch. Surg. 67 645 1953.)



Fig 404 (*Left*) Clinical photograph of an 11½-month-old child bearing a malignant ganglioneuroma of the ganglion nodosum of the right vagus nerve (*Right*) Roentgenographic appearance of the cervical malignant ganglioneuroma. Note the mottled regions of calcification scattered throughout the tumor (Case report No 70) (Pack, Ariel, and Miller, A M A Arch Surg 67 645, 1953)

of her neck which was first discovered when she was 6 months of age It was at first believed by the local physician to represent an inflammatory lymph node, but the cervical tumor grew steadily in size An aspiration biopsy examined by Dr George Erdman revealed immature neural elements, a diagnosis of cervical neuroblastoma was made on the basis of this biopsy (Fig 406) and was confirmed by Dr George Higgins The patient was treated by her local physician with deep x-ray therapy to the cervical mass with no diminution in its size She received 2000 r in air delivered in 30 days to a 6 × 8 cm port The factors were as follows 200 kv, 20 ma , 50 cm T S D , 9 5 mm Cu and 1 mm Al filter, and H V L 1 cm

The patient was first seen by us on November 5, 1952, at which time she was at the height of an erythematous reaction resulting from the irradiation A mass 5 cm in diameter was palpated deep in the right cervical region with posterior fixation and without attachment to the skin (Fig 404) It was ovoid in contour and discrete Although not attached to its contiguous structures, it was immobile because of deep fixation A sign of interest was the anterolateral displacement of the carotid artery The trachea was not displaced, and the patient breathed, swallowed, and cried normally

Physical examination was otherwise normal except for an incidental finding of three congenital hemangiomas, one situated over the glabella and two on the left side of the neck No abdominal masses were palpable and the eyes were normal in every respect

Her past history was normal except that five weeks before the patient was seen by us, she had fallen out of bed, injuring her right thigh This injury resulted in a fracture of the distal shaft of the right femur, diagnosed by a skeletal roentgenographic survey performed at a later date The remainder of the skeletal roentgenograms were negative for evidence of bony metastases A roentgenogram of the cervical region revealed mottled calcification within a deep soft-tissue mass (Fig 404, *Right*)

Her family history was negative for cancer The child's birth was a full-term, normal, spontaneous delivery Her birth weight was 6 lbs , 12 oz Her development and growth were normal in every respect She

had no childhood diseases Her mental development was normal

The preoperative diagnosis was cervical neuroblastoma. The question of whether this represented a primary neoplasm or a metastatic deposit presented itself The rarity of cervical neuroblastomas coupled with the recent fracture of her femur might suggest this to be a metastasis Roentgenograms of the femur however showed no osteolysis and the fall which she had sustained was of sufficient severity to produce a traumatic fracture. The absence of any other evidence of neoplasia further indicated that the tumor was a primary one It was accordingly decided to wait for subsidence of the erythematous radiation reaction and then to attempt surgical extirpation of this cervical neoplasm

Operation

This was successfully accomplished on November 26 1952 A longitudinal incision over the right sternocleidomastoid muscle with severance of this muscle permitted exposure of the neoplasm, which presented as a smooth ovoid tumefaction measuring 5 × 3 cm nestled within the carotid sheath It was dissected free of contiguous tissues with difficulty especially anteromedially where it was attached to the vagus nerve The right vagus nerve was pushed anteriorly and the tumor lay posteriorly and laterally to the nerve pushing it forward. The site of the tumor and its intimate relationship with the vagus nerve were identical with that of the nodose ganglion from which it originated. The carotid arteries and the jugular vein were also pushed anteriorly in front of the tumor which made the dissection somewhat difficult The internal carotid was attenuated and stretched over the superomedial pole of the tumor and constituted a considerable surgical hazard. The tumor compressed the vagus nerve the glossopharyngeal nerve and the sympathetic ganglia and nerves of this region The superior pole of the tumor was close to the main trunk of the facial nerve, which was slightly traumatized during the dissection By sharp dissection the tumor was dissected free and removed *in toto* The subjacent nerves were gently compressed when the tumor was removed, but they were not particularly frayed or thinned.

Pathologic Examination

The tumor was an ovoid mass which measured 5 × 3 5 × 3 7 cm It was reddish brown in color intermottled by yellowish flecks The external surface presented a shaggy structure composed of numerous fibrous strands. On sectioning, the cut surface presented numerous yellowish necrotic foci intermingled with the reddish-brown surface (Fig. 405)

The following description of the histologic features of this malignant ganglioneuroma presents the appearance of structures as observed under very low magnification gradually increased to higher magnifications It was prepared with the cooperation of Dr George Higgins, pathologist of the Pack Medical Group

With the scanning lens the tumor is found to be divided by rather coarse strands of collagen into lobulations often incomplete which may measure up to one two or more millimeters (Fig 407) At the periphery these fibers intermingle with those which form the capsule Foci of necrosis occupy the central region of many lobules in these slight calcification is suggested by a faint basophilic reaction At



FIG 405 Malignant ganglioneuroma. Gross appearance of the ganglioneuroma in Fig 404 which had been dissected from the nodose ganglion of the right vagus nerve. Although histologically malignant, the tumor appears well encapsulated. (Case report No. 70) (Pack, Ariel, and Miller A.M.A. Arch. Surg. 67 645 1953)

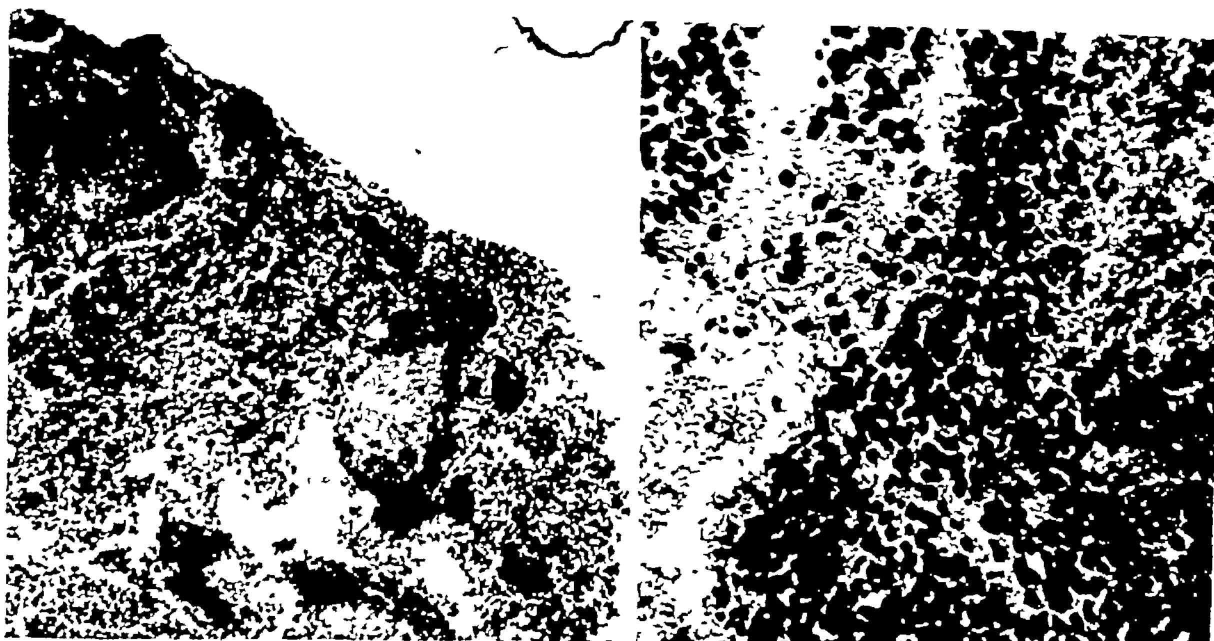


FIG 406 Malignant ganglioneuroma (*Left*) Low-power photomicrograph of the aspiration biopsy from the cervical tumor (Fig 405) upon which a diagnosis of neuroblastoma was suspected Foci of necrosis are located within sheets of poorly differentiated cells (*Right*) Higher-power magnification of left figure Note the poorly differentiated neuroblastomatous cells with differentiated ganglionic cells interspersed throughout Necrotic regions are seen (Case report No 70) (*Courtesy*, Dr George Erdman Pack, Ariel, and Miller, A M A Arch Surg 67 645, 1953)

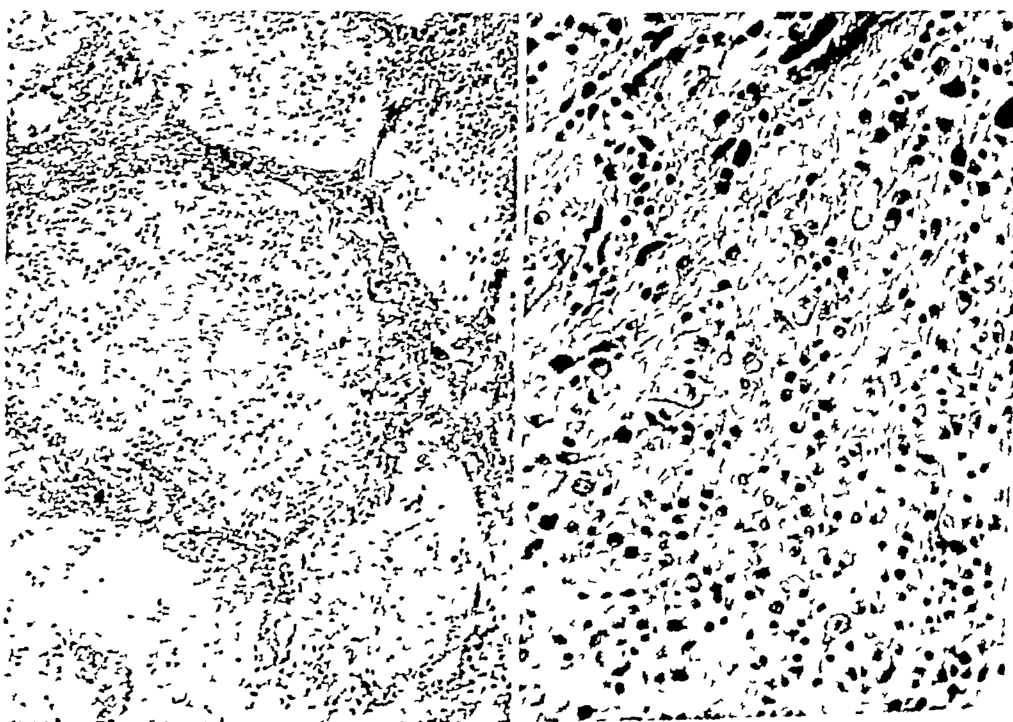


FIG 407 (*Left*) Malignant ganglioneuroma A very low-power photomicrograph of a malignant ganglioneuroma The lobules are separated by collagen fibers The central regions of the lobules are frequently necrotic There is a relative paucity of cells The larger cells scattered throughout are ganglion cells (*Right*) Low-power photomicrograph of one region of a malignant ganglioneuroma which consists of completely and partially differentiated ganglionic cells (Case report No 70) (Pack, Ariel, and Miller, A M A Arch Surg 67 645, 1953)

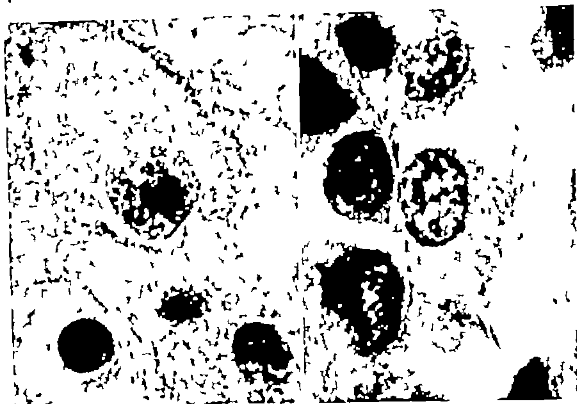


FIG. 408. Malignant ganglioneuroma. (*Left*) High-power photomicrograph of several cells shown in Fig 407 demonstrating differentiated ganglion cells. (*Right*) High-power photomicrograph of several cells shown in Fig. 407 demonstrating several partially differentiated ganglion cells. (Case report No 70.) (Pack, Ariel, and Miller A.M.A. Arch. Surg 67 645 1953.)

this magnification large ovoid and elongated cells suggesting nerve cells and portions of neurons are identifiable, but their number varies greatly from field to field with no areas in which they are absent

Increased magnification shows the resemblance of these ovoid and elongated cells to the nerve cells of the sympathetic ganglia (Fig 408) They represent differentiated ganglion cells Although most tend to be smaller some reach a length of 50 microns or more The cell body with its finely granular pale, acidophilic cytoplasm may assume either a globular oval, pyriform, spindle, or polygonal shape Pointed cytoplasmic processes extend for variable distances into the surrounding areas and converge with numerous nerve fibers which are not recognized as entities without special staining technics Typically a single nucleus lies in the center of the cell. Not infrequently two and occasionally three are present and are located in an eccentric or even peripheral position The nuclear membrane is thin and delicate Chromatin lies in fine aggregates and is scanty giving the cell a pale appearance unless pyknosis has developed. The large, prominent, dark staining nucleolus usually single tends to lie in an eccentric position In the partially differentiated cells the cytoplasm is less abundant and may lose its acidophilia and fibers. The nucleus tends to be larger with a more prominent nuclear membrane and coarsening of the chromatin granules the nucleolus remains prominent As undifferentiation proceeds the cells tend to become smaller until they approach the type characteristic of neuroblastoma. The cytoplasm becomes very scant and scarcely stains acidophilic. The nucleus comprises most of the cell, is usually spheroidal in shape outlined by a rather thick nuclear membrane and dense with a large amount of dark staining chromatin material (Fig 409) Delicate neurofibrils may be seen, but they are not nearly so much in evidence as in the more differentiated variety No pseudorosettes were seen in this specimen The aspiration biopsy in this patient yielded tissue which presented these histologic characteristics A diagnosis of neuroblastoma was accordingly made on the basis of the aspirated material but was modified to malignant ganglioneu

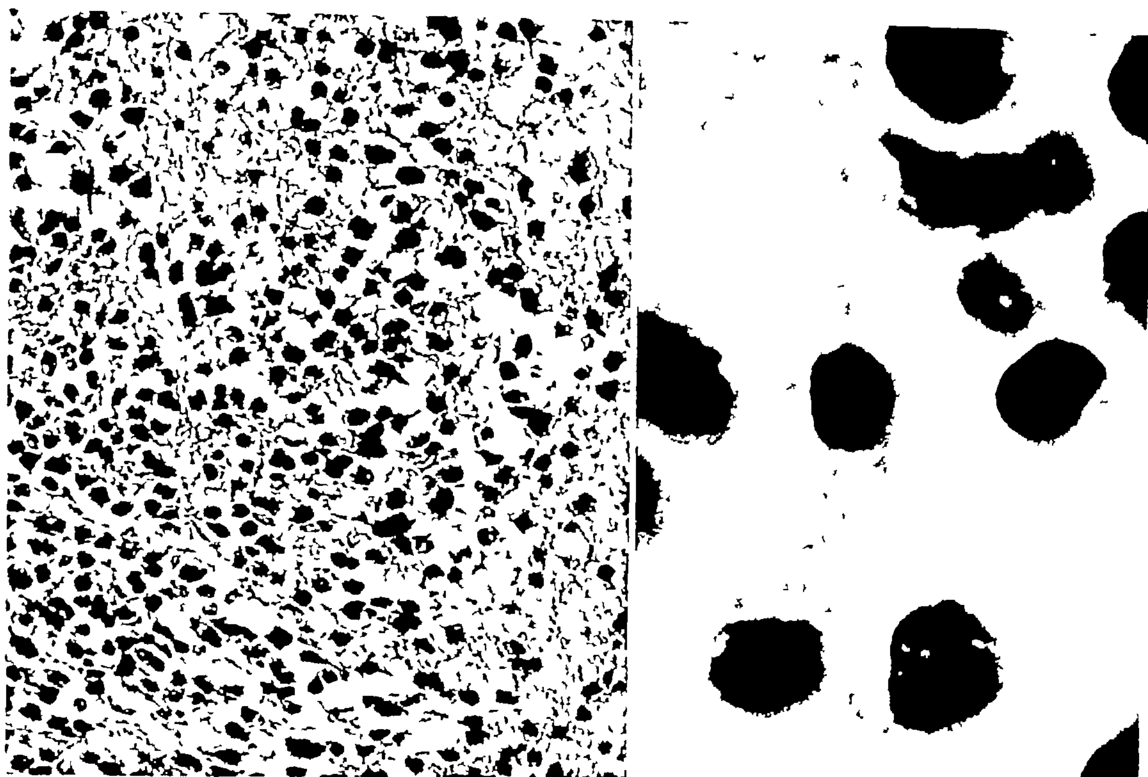


FIG 409 Malignant ganglioneuroma (*Left*) Photomicrograph demonstrating a region of undifferentiated, primitive, hyperchromatic cells surrounded by a loose network of delicate nerve fibrils Note the resemblance of this section to the original aspiration biopsy specimen (Fig 406) (*Right*) High-power magnification of the cells in left figure, showing the details of the cellular structure The cells are smaller and pleomorphic The nucleus is large, high in chromatin, eccentrically placed, and has a prominent nuclear membrane The cytoplasm is scanty (Case report No 70) (Pack, Ariel, and Miller, A M A Arch Surg 67 645, 1953)

roma after the entire tumor was available for examination There is a more or less diffuse intermingling of benign and malignant elements

Unlike normal nerve cells, changes of senescence are evident in a larger number and are manifested by the outer rim of the cell's (ectoplasm) staining more intensely and gradually developing an increasingly basophilic tinge The nucleus stains more homogeneously, with loss of internal details, but the nucleolus remains distinct until the degenerative process is advanced

Small cells with dark, elongated, fusiform nuclei which resemble fibrocytes and represent the nerve sheath cells (Schwann cells) may occasionally show neoplastic changes The nuclei of satellite cells (oligodendroglia, astrocytes, etc) are seen routinely but are not prominent in sections stained by routine methods

The cells lie in an acidophilic stroma composed of nerve fibers arranged densely in some areas and rather loosely in others Although they appear finer, shorter, and have a more diversified direction (lattice pattern) than collagenous fibers, they are most easily identified because they appear continuous with the cell cytoplasm

The blood vessels are not numerous and appear prominent only in the trabeculae

Foci of necrosis are frequent, presenting a coarsely granular appearance, and are the site of calcium deposits, evident as blue granules or plates which tear the adjacent friable tissues during the preparation of the section

Postoperative Course

The patient's postoperative course was complicated by difficulty in breathing due to paralysis of the laryngeal musculature, inability to swallow foods or fluids, ptosis of the right eyelid due probably to damage to the cervical sympathetic ganglia and nerves, and right facial hemiparesis due to surgical trauma to the facial nerve Some of these symptoms were due to trauma to the right vagus nerve Since none of the

major nerves was severed during the operation it was believed that the symptoms were the result of surgical manipulation of the nerves as well as discission of some of the smaller anastomosing neurons It was believed that the disturbances would be temporary A tracheostomy was performed under local anesthesia on the first postoperative day because of inability to swallow and cough due to anesthesia of the hypopharynx and larynx resulting in regurgitation, aspiration and dyspnea. Attempts to feed the patient by an indwelling nasogastric tube were unsuccessful as the patient regurgitated at sporadic intervals and continued to cough up thick mucoid secretions. She developed a bronchopneumonia and atelectasis on the right side and was treated by antibiotics (penicillin and Terramycin) and Tryptar spray into the bronchial tree through the tracheostomy tube. Her general condition improved, but because she remained unable to swallow a Janeway gastrostomy under local anesthesia was performed on December 10 1952 She was discharged from the hospital on December 31 1952, and was readmitted on March 24 1953 at which time the tracheostomy tube was removed. The facial palsy was first to disappear later the cough reflex reappeared, and swallowing without regurgitation and aspiration became possible The child can now breathe, swallow and smile normally

Discussion of Case Report No 70

There have been three reported cases of ganglioneuromas arising from the nodose ganglion of the vagus nerve. Benda in 1904 reported and described a pathologic specimen of such a neoplasm obtained from an inoperable, apple-sized mass from the right cervical region of a child who subsequently died The clinical features are not presented This case was similar to the one reported here in that both arose from the right ganglion nodosum In another case reported by Clay in 1950 the tumor arose from the left nodose ganglion of the vagus nerve in a 21⁄ year-old girl. This tumor was successfully resected, necessitating the transection of the vagus nerve with a subsequent neurorrhaphy The child has a persistent left vocal cord paralysis Both of the previously reported cases of ganglioneuroma of the ganglion nodosum were reports of benign tumors presenting fully differentiated, large, ganglion cells The tumor of our report differs in that it was essentially a malignant tumor containing every variant of ganglionic structure, from the large and at times multinucleated cells to small, anaplastic cells with large nuclei and scanty cytoplasm.

It must accordingly be designated as a malignant ganglioneuroma containing both benign ganglioneuromatous and malignant neuroblastomatous elements

Shumacker and Lawrence, after reviewing the literature of cervical ganglioneuromas, summarized the significant clinical characteristics of these tumors and described them as consisting of a slowly growing, asymptomatic mass beginning early in childhood, fixed to deeper structures, the overlying skin riding freely over the tumor with repositioning of the carotid artery to a superficial site. They state that wherever the position of the carotid artery is recorded, it is described to be superficially placed. The patient herein reported manifested this symptom complex.

Relationship of the Neuroanatomy of the Vagus Nerve to Symptoms Produced by Tumors of the Vagus

In order to understand the origin of ganglioneuromas of the ganglion nodosum of the vagus nerve and to appreciate the clinical sequelae which result from severance of the vagus nerve during resection of the ganglion nodosum a brief description of the neuroanatomy of this structure will be presented.

Embryologically the vagus nerve which is composite takes origin from



FIG. 410 (*Left*) A mediastinal ganglioneuroma situated in the posterior mediastinum of a 35-year-old female. (*Right*) The postoperative roentgenogram shows a normal chest following the resection of the ganglioneuroma which was well encapsulated and resected with relative ease. (Case report No. 71)

health examination program a mass was found occupying the inferior posterior mediastinum. It was protruding into the right chest. It occupied the right vertebral gutter

Treatment

On December 11 1946 a posterior mediastinotomy was performed. A firm, encapsulated tumor weighing 80 gm and measuring 8 × 7 cm was surgically removed The operation was performed extrapleurally

Microscopic study revealed the tumor to be a ganglioneuroma. There were both fairly large and small clusters of ganglion cells No mitotic figures were seen Convalescence was uneventful. She had some postoperative intercostal pain but is in good health to date

CASE REPORT NO 72: RETROPERITONEAL GANGLIONEUROMA

D D S a 16-year-old girl experienced backache in her loin and pelvis. In January 1932 in a distant city an exploratory laparotomy was performed, and a retroperitoneal tumor was encountered which was pronounced to be inoperable. A biopsy taken at the time of laparotomy was diagnosed as benign ganglioneuroma. During the succeeding eleven years the tumor gradually increased in bulk so that it was readily palpable in the abdomen, and during this time the backaches became more severe and there were edema and swelling of the left ankle and leg

When first examined by us in 1941 the 27 year-old patient had a huge semifixed retroperitoneal tumor extending deep into the pelvis and superiorly to the level of the second lumbar vertebra in the left iliac quadrant. Cystoscopic and pyelographic studies revealed an enormous hydronephrotic left kidney due to extrinsic ureteral obstruction by the mass. Barium enema and roentgenograms of the colon showed displacement and distortion of the colon but no true invasion of the bowel



FIG. 411 The surgical specimen of a massive retroperitoneal ganglioneuroma which was successfully resected. (Case report No. 72.)

Treatment

On June 20, 1941, an incision was made in the groin upward and laterally to expose the retroperitoneal space A multilobular tumor was carefully dissected from the iliac vessels and paravertebral regions Four pints of blood were administered during the operative procedure The excised tumor measured 20 × 12 cm in diameter and was encapsulated and coarsely lobulated The microscopic diagnosis was ganglionic neuroma A left nephrectomy was later performed

Fifteen years later the patient was in good health with no evidence of recurrence There was some elephantiasis of the left leg and thigh

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NEUROBLASTOMA (SYMPATHICOBLASTOMA) *

The neuroblastoma is a highly malignant neoplasm which has attracted the attention of pathologists for many years but because of its rarity and usual fatal course adequate clinical studies have been wanting. With few exceptions patients on whom this diagnosis is established suffer fatal outcomes. Betterment of end results for other types of malignant neoplasms has been achieved by careful analyses of all factors pertaining to the disease to note which contributed to the poor end results. Correction of these factors combined with improvements in surgical and radiologic techniques has enhanced markedly the prognosis for many forms of cancer. Unfortunately this is not the case for neuroblastoma. Due largely to the highly malignant nature of the neoplasm and its early widespread metastases, the onset of the disease is often heralded by clinical manifestations secondary to these metastases. A prolonged time usually elapses before the existence of the primary neoplasm is discovered. Therapeutic attempts are frequently fraught with failure because the neoplasm is usually widespread when the patient is first observed.

DEFINITION AND NOMENCLATURE

Neuroblastomas in this presentation consist of that group of tumors which are derived from the primitive nerve cell (neuroblast). The tumors are confined almost exclusively to the sympathetic nervous system and originate most frequently in the adrenal medulla.

Bailey and Cushing in 1928 suggested that for the undifferentiated tumors of the sympathetic nervous system the term *sympathicoblastoma* would be more desirable than *neuroblastoma* as the latter is also used to describe certain cerebral neoplasms. They point out that all the cells of the tumor are not potential neuroblasts since some may differentiate into chromaffin cells. They believe the term *sympathicoblastoma* to be more suitable, as it suggests a malignant tumor taking origin from pluripotential cells of the sympathetic system. In this presentation the terms *neuroblastoma* and *sympathicoblastoma* are used synonymously because of the widespread use of both names for the neoplasm.

The two well known clinical syndromes of Pepper and Hutchinson were described in 1901 and 1907 respectively. Pepper described a coexistent and congenital sarcoma of the liver and suprarenal gland. He had studied the cases of six girls with extensive metastatic involvement of the liver but without metastasis to bone. In this group three primary lesions were located in the right adrenal gland. Hutchinson in 1907 presented seven cases and three from literature to demonstrate a primary neoplasm of the adrenal gland which produced metastases commonly in the bones of the skull. Farber demonstrated that the location of metastases is not affected by the site of the primary tumor nor by its degree of anaplasia and suggested that the use of the terms *Pepper* or *Hutchinson syndrome* be discontinued.

INCIDENCE

There have been approximately 450 cases of neuroblastoma reported in the literature to date.

During the twenty year period from 1931 to 1950 inclusive there have been 14 patients with neuroblastoma observed by the authors from a series of

* In collaboration with E Douglas Horning

approximately 20,000 cases, chiefly of neoplastic diseases This incidence fits in well with those observed at other large centers

Although relatively rare, these tumors nevertheless comprise one of the most frequent abdominal neoplasms observed in infants and children under 4 years of age Blacklock (1934) reported a series of 100 consecutive malignant tumors seen in children under the age of 12 and found new growths arising from the autonomic nervous system to be fourth in the order of frequency Wittenborg observed 143 neuroblastomas recorded at the Children's Medical Center of Boston

SEX AND AGE DISTRIBUTION

There is no sexual predilection

The average age of the patients studied by the authors at the onset of symptoms was 3 1 years The youngest was a male aged 3 months, and the oldest a male aged 9 years Neuroblastomas are essentially a malady of infants and have been described as occurring in prenatal life Pepper (1901) pointed out the prenatal occurrence of these tumors in his paper "Congenital Sarcoma of the Liver" Wright (1910), and Landau (1912), Lewis and Geschickter (1934), and Potter and Parrish have each reported a case occurring in a stillborn Reid (1928) found over 80 per cent in patients under 2½ years of age, and Blacklock (1934) stated that the sympathicoblastomas were the most frequently seen tumors arising from the sympathetic nervous system and were most common in the second year of life Scott and Oliver (1933) asserted that the tumors giving rise to bony metastases usually occur at a somewhat later age, about 6 years Lewis and Geschickter (1934) called attention to the fact that neuroblastomas develop also in adults Five of their series developed in patients over 15 years of age, one in a man 45 years old Meltzer (1926) reported two cases in adult males aged 40 and 53 Other more recent reports also describe the occurrence of neuroblastomas in adults Ballard reported an instance of neuroblastoma occurring in a subject 69 years old

ETIOLOGIC FACTORS

The observation that these tumors occur so early in life suggests a congenital relationship and serves to support Cohnheim's theory of tumors originating in cell rests Kohn in 1907 demonstrated that neuroblasts emigrate from the ganglionic rest of the medullary tube along the anterior spinal segmental nerve to form the various plexuses and the medulla of the adrenals Bielchowsky observed that sympathogonia, from which the medulla of the adrenal gland takes origin, begins to invade the analog of the adrenal cortex—of mesoblastic origin—during the eighth week and subsequently aggregates in its center This migration continues throughout fetal life and after birth until puberty As a result of the long path of migration of these primitive nerve cells, groups of them occasionally are displaced and so become the potential origins of tumors at a later period The observation that the neuroblastomas arise not only from the adrenal medulla but also from other paraganglionic tissue, such as that adjacent to the adrenal glands, the superior cervical sympathetic ganglion, sympathetic tissue at the root of the lungs, and retropleural and retroperitoneal locations, with invasion of the extradural space surrounding the spinal cord in some instances, indicates that neuroblastomas may arise from all tissues of the sympathetic nervous system

There are no factors, such as trauma, infection, etc, to account for the production of neuroblastomas. The frequent statement that trauma excited the

onset of symptoms is no doubt related to the fact that trauma probably in duced such changes in a subclinical neoplastic deposit as to make the neoplasm manifest clinically An example would be the production of ecchymosis by trauma in a metastatic neuroblastoma of the calvarium.

PATHOLOGIC ANATOMY

Grossly the tumor is often large and occupies a great portion of the abdominal cavity It consists of pink, firm tissue which cuts with a gritty sensa tion due to foci of calcification. The surface is mottled by hemorrhagic areas. Cut section reveals a firm, smooth greyish pink surface which presents an interlacing maze of fibrous strands Smaller and larger regions of hemor rhagic necrosis are scattered throughout the section. Thin-walled capillaries, the source of the ecchymosis which so often is the first sign of the disease, may be noted.

The liver when the seat of metas tases, may be very large with most of it replaced by a huge, pinkish-grey nodular mass which is usually of fi sistency with a pseudocapsule, o be studded with multiple small and red nodules from 1 to 2 diameter

Lymph node metastases are discrete, nodular and of firm ency They are seldom fluct tender They bear a clinical rese to lymphomatous tumors.

The morphologic appearance characteristic. The tumors resem coma and were formerly term *coma of children* The cells a and round and contain but litt plasm, with large, central, hy matic nuclei they resemble th tive cells of the sympathetic system. It has been stated t younger the patient, the less tiated are the cells in the compo the tumor and also the grea malignancy In the very young mor is composed of the small undifferentiated cells, while i patients the cells become polyg spindle-shaped and tend to form mature cell type. Occasionally occur in which all three types of

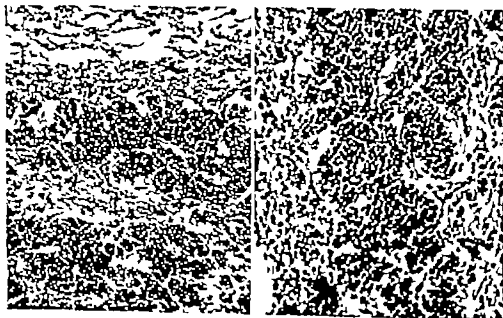


FIG. 412. Neuroblastoma. (*Left*) Histologic appearance of intraabdominal neuroblastoma, demonstrating the sheets of cells surrounded by variable amounts of fibrous-tissue stroma. (*Right*) Histologic appearance of the neuroblastoma shown in left figure, with higher magnification disclosing rosette formation. (Pack, Horning, and Ariel, J Neuropath. & Exper Neurol. 11:235 1952.)

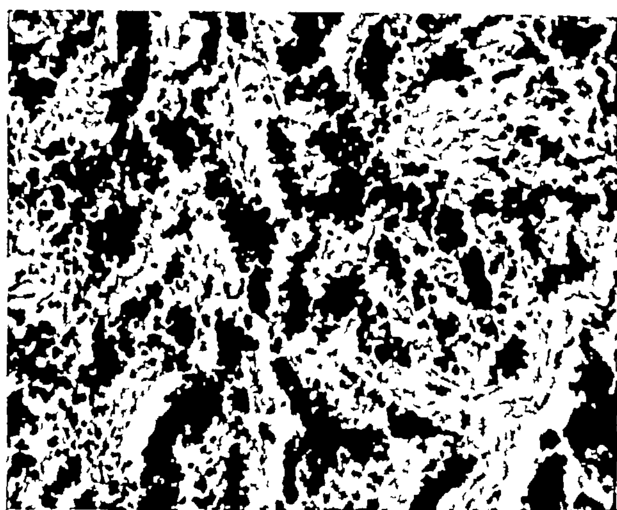


Fig 413 Histologic appearance of neuroblastoma Note the small, round cells, scanty cytoplasm, and hyperchromatic nuclei occurring in small islets separated by a fibrillar stroma (Pack, Horning, and Ariel, J Neuropath & Exper Neurol *11* 235, 1952)

arising from the sympathetic system are noted and all three stages of differentiation of the formative neuroblast may be observed The metastases are composed usually of small, round cells, often with no fibrillar stroma The in vitro studies of Murray and Stout have enhanced greatly an understanding of the nosology of these tumors

Ewing stated that the structure varied in the degree with which nerve elements are developed In the least mature types there are imperfect rosettes, very numerous but ill-defined fibrils giving an abundance of hyaline stroma, or many hyaline globules staining with eosin The hyaline globules resolve themselves into bundles of imperfect nerve fibrilli connecting groups of neurocytes Various other structures may be interpreted as imperfect ganglion cells, axis cylinder processes, or glia fibrils

Stout believes that many reported cases of sympathicoblastomas are actually partially differentiated ganglioneuromas

METASTASES

Neuroblastomas may invade the fibrous capsule and extend by direct infiltration into contiguous structures More frequently, however, they may disseminate by means of the blood stream and involve any organ within the body They infiltrate by means of permeation or embolic spread into the lymphatics and deposit metastatic foci in lymph nodes or organs drained by the lymphatics It is these diverse routes of metastasis which led Pepper in 1901 to stress metastases to liver and Hutchinson to stress skull involvement.

Blacklock in 1934 described the mechanism whereby the tumor invades the fibrous capsule and blood vessels and extends thereby into the upper abdomen, producing involvement of the liver, the kidneys, intestines, regional lymph nodes, diaphragm, pancreas, and vertebrae He believed this spread by means of local extension to be the most common route of progression, and metastasis by means of the lymphatics the next most common Dissemination by means of the blood stream, although of course the most serious, he believed to be the third in frequency Blacklock further reported that liver involvement results from direct invasion of the portal system, which results in scattered nodules throughout the substance of the organs, associated with bony metastases which are most frequently seen in the skull, and are commonly associated with the invasion of the organs It is surprising that with this degree of bony metastases, pulmonary metastases are seen relatively infrequently Pulmonary invasion was observed in only two patients of this series

Chandler and Norcross in 1940 demonstrated invasion into the spine with spinal nerve and cord symptoms, and in one of our own cases the tumor was found to have invaded the spinal cord at laminectomy

The metastases occur early in the clinical course, and all of the authors' patients showed evidence of metastatic deposits when they first presented themselves for treatment The site of the pri-

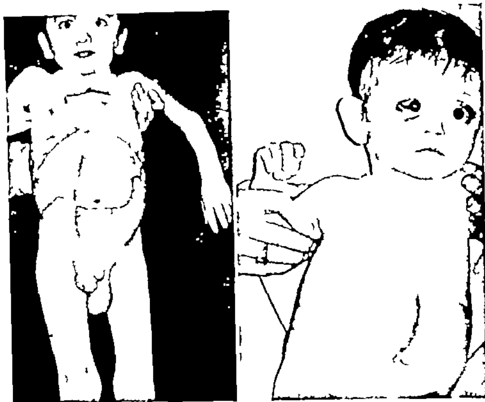


FIG 414 Neuroblastoma. (*Left*) Distended abdomen, due to a large intraabdominal neuroblastoma which invaded adrenals, pancreas and liver and metastasized to bone Patient succumbed 8 months after diagnosis. (*Right*) Intraabdominal neuroblastoma which metastasized to the orbit producing typical ocular signs. (Pack, Horning, and Ariel J Neuropath. & Exper Neurol *11*:235 1952.)

mary neoplasm or its histologic characteristics could in no way be found attributable for the site or number of metastases Bothman and Blankstein in 1942 believed that the metastatic route depends more on the age of the patient than on cell type

SYMPTOMS

The early and widespread metastases resulting from this deep-seated tumor result in protean and bizarre clinical expressions The initial target organ or structure is not infrequently distant from the primary neoplasm, which may be quiescent from a symptomatic standpoint The initial symptoms may be fever and anemia with no localizing signs but more frequently fever and anemia accompany an abdominal mass eye symptoms or other localizing lesions It is indeed surprising that both adrenals may appear completely invaded by the neoplasm but that symptoms of hypoadrenalism (Addison's disease) are extremely rare although they have been reported No abnormalities in sexual development or other metabolic defects resulting from increased adrenalism were observed Lewis and Geschickter noted that fever anemia, and an abdominal mass were the most common findings and described episodes resembling acute rheumatic fever including joint pains

Ecchymosis of the eyelids, with or without proptosis is frequently the signal symptom, and enlarged lymph nodes may herald the presence of neuroblastoma. Anemia was present in all patients of this series when they were first observed. Several authors have commented upon the differences of age in patients with bone involvement from those with liver invasion Those with bone involvement are younger than those with hepatic metastases

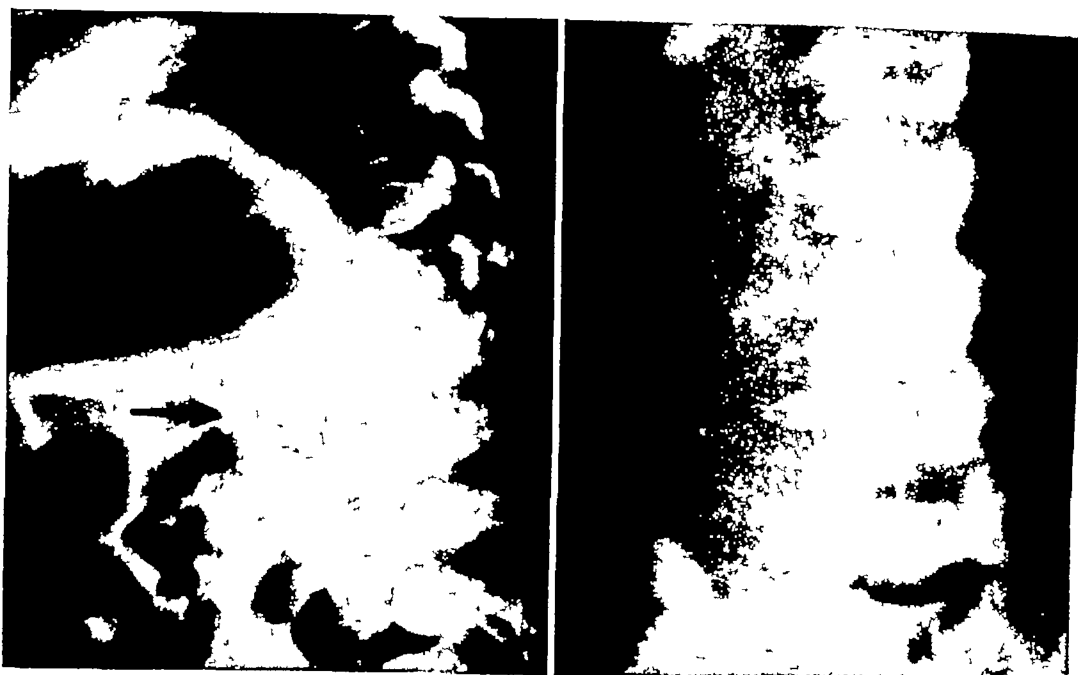


FIG 415 Neuroblastoma Roentgenograms demonstrating calcification in a large intraabdominal neuroblastoma (Pack, Horning, and Ariel, J Neuropath & Exper. Neurol *11* 235, 1952)

DIAGNOSIS

The establishment of the diagnosis of neuroblastoma and its differentiation from other neoplasms are difficult In all but one of our 14 patients, a diagnosis of other diseases was made elsewhere, and a considerable time elapsed from the onset of symptoms until the final diagnosis of neuroblastoma was established The abdominal swelling which is frequently the presenting symptom must be differentiated from appendiceal abscess, ovarian tumors, Wilms's tumor, and other intraabdominal space-occupying masses Fever in children, associated with anemia, has frequently caused a mistaken diagnosis of rheumatic fever to be made The presence of osteolytic lesions of bones has been erroneously diagnosed as Hand-Schuller-Christian disease, or Ewing's sarcoma Evidence of disability involving the lower extremity, *associated not infrequently with neuro*logic adnormalities of the urinary or gastrointestinal tract, suggests the possibility of spinal cord tumors

The characteristic feature of an intraabdominal mass containing calcific deposits is suggestive of neuroblastoma but must be distinguished from tuberculous lymphadenitis and old hematomas or abscesses Not infrequently the neuroblastoma announces its presence by lymphadenopathy, either cervical or inguinal, simulating lymphoblastoma, and indicates that careful evaluation of the hematologic findings is essential to differentiate neuroblastoma producing lymph node metastases from the various lymphomas

The frequent presence of ecchymosis, proptosis, and other clinical manifestations of orbital metastatic deposits resulting from neuroblastomas necessitates a differential diagnosis from primary orbital tumors.

X-RAY APPEARANCES

The protean nature of neuroblastoma results in diverse and varied roentgenographic evidences of the neoplasm The primary tumor may produce an increased abdominal roentgen opacity which may present evidence of calcification

Pyelograms frequently give evidence of pressure upon the kidneys or ureters Roentgenograms of the chest may reveal

a mediastinal mass and to a lesser extent discrete metastatic deposits in the lungs

Metastatic deposits in the osseous system present a most characteristic roentgenographic picture Areas of resorption, usually distal to the epiphyseal line, are noted, these may be wedge shaped, extending from the cortex into the cancellus bone or minute and spotty to give a moth-eaten and mottled appearance Involvement of the calvarium is found to be more common than involvement of the base of the skull. Bothman and Blankstein described localized foci of increased density in the skull and in the pelvic and long bones They further described a "characteristic new subperiosteal proliferation in the long bones producing a roentgen appearance of whiskers or fringes due to perpendicular lines formed by the bony spicules" Multiple bony metastases are not infrequently observed.



FIG. 416 Neuroblastoma. Roentgenograms demonstrating metastasis to tibia from a neuroblastoma which presented itself as an occipital swelling Patient succumbed 12 months later (Pack, Horning, and Ariel, J Neuropath. & Exper Neurol *11* 235 1952.)

TREATMENT

Neuroblastoma to be cured must be diagnosed early and treated radically A combination of surgical excision and irradiation, carefully planned and meticulously applied, is essential for the treatment of this cancer The wide individual variations manifested by the tumor's sensitivity to irradiation indicate the need for precise and painstaking planning in the preparation of the therapeutic regime. Wittenborg reported complete regression of a neuroblastoma with as small a tumor dose as 400 r delivered in sixteen days but viable tumor was found at postmortem in other instances after a tumor dose of 1200 r had been administered. In the 14 cases reported by the authors, the patients received large tumor doses of irradiation and no cures were obtained These features emphasize the marked variations in radiosensitivity manifested by neuroblastomas

Almost all of the patients observed at the Children's Hospital in Boston who survived 3 years or more received a tumor dose of 800 to 1200 r in ten to fourteen days usually followed by a second course in about three months Although the majority of neuroblastomas are radiosensitive, because many viable tumor cells may be present even after radical courses of irradiation, sole reliance for cures should not be placed upon irradiation. The best method of treatment consists of radical surgical extirpation followed by immediate postoperative irradiation. Treatment should be started on the day of operation at which time an initial dose of 200 r in air is delivered to the skin, and a total course of 1400 r to 1800 r in seven to ten days is delivered. Wound breakdown has never been noted on this re-



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FIG. 416. Neuroblastoma. Roentgenograms demonstrating metastasis to tibia from a neuroblastoma which presented itself as an occipital swelling. Patient succumbed 12 months later (Pack, Horning, and Ariel, J Neuropath. & Exper Neurol. 11·235 1952.)

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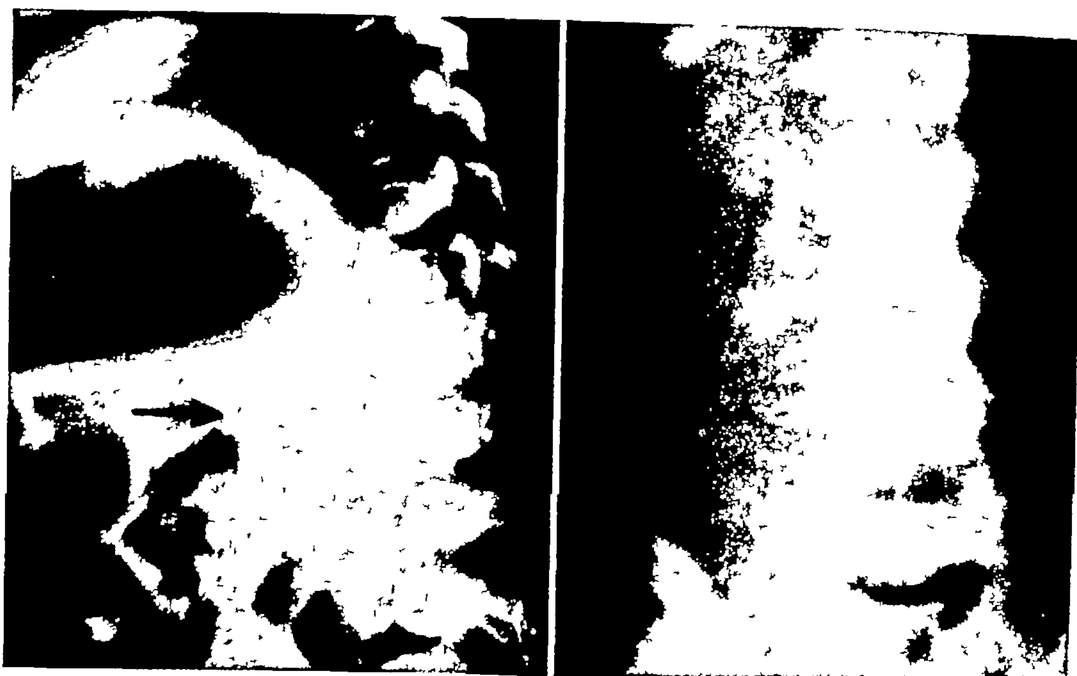


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gime The limiting dosage factor in the treatment of infants and small children is not the skin but the lability of the hematopoietic system, postmortem examination of the vertebrae within the direct field of radiation shows marked fibrosis Preoperative irradiation is not indicated in most instances

Palliative effects may be obtained by a variety of methods Tumors may frequently engulf the urinary system, producing obstruction to the free flow of urine and causing the patient to succumb from uremia This possibility must constantly be borne in mind, with all efforts directed toward preventing any compromise with the urinary output Radiation therapy can usually cause sufficient regression in the tumor to disengage any obstruction to the ureters, bladder, or kidney

END RESULTS

Examination of reports of prolonged survival indicates that only patients who had localized abdominal masses and, surprisingly enough, patients who had metastases to the liver, may be cured The good results achieved in some instances indicate that palliation and even cures may be achieved and emphasize that large abdominal tumors and liver metastases need not deter the surgeon or radiotherapist from instituting a radical course of therapy in the hope that a cure may be achieved The recent advances of surgical attack upon the liver may further improve these results, and liver metastases of neuroblastoma may possibly be resected Contrariwise, in no instance in which bone metastases had been demonstrated were cures achieved

Ewing has commented upon the observation that neuroblastoma may undergo spontaneous hemorrhage and necrosis and then disappear without any treatment other than biopsy A neuroblastoma may also undergo spontaneous differentiation and become a *benign* ganglioneuroma Removal of the tumor should be effected without delay after a short period of 24 to 48 hours of well-organized diagnostic study and preoperative preparation

Hung and O'Flanagan have reported a four-year cure in a 27-year-old pregnant female They emphasized a cure by surgical excision of the tumor, including the kidney, and commented upon the better prognosis which may obtain in the older age groups Lehman reported a fifteen-year cure for a neuroblastoma treated by surgical excision Boyd observed six cases of neuroblastoma at the Vancouver Hospital from 1945 to 1948 He related the story of three patients whose neuroblastomas responded favorably to radiation therapy, with disappearance of the masses completely in four to six weeks after the onset of treatment He considered the improvement to be only temporary In his experience the patients who had the tumor on the left side received a satisfactory response to irradiation, and those patients who had the tumor on the right side tolerated the treatment poorly and had much nausea and progressive anemia

Shaffer reported the treatment of two patients by radioactive phosphorus, he observed that it had no effect upon one who received it by intravenous administration Shaffer concluded that in his experience radioactive phosphorus was not valuable

No patients were seen by the authors at a time when the tumor could be resected In five instances attempts at surgical procedures were instituted, but the tumors were found technically inoperable, and either nothing was done or the tumor was partially excised In each instance surgical treatment was followed by postoperative irradiation All treatment by irradiation was rewarded by a prompt response which was manifested by a shrinkage of the tumor mass and, as a rule, general improvement of the patient In two in-

stances the tumors were found radio-resistant, and even after relatively large doses of roentgen rays there was only slight shrinkage of the masses These particular tumors were extremely malignant, and the patient in each instance succumbed shortly after the therapeutic attempt. The radiation factors which were generally given consisted of roentgen rays generated at 250 kv 25 ma. 1 5 mm. copper filtration and 50 cm. target-skin distance A daily dose varying from 100 to 300 r per port was generally given and attempts were made to deliver a course of therapy totalling 2000 r units in from 14 to 20 days The limiting factor for the deliverance of roentgen radiation was the severe damage to the hematopoietic system All patients presented themselves with anemia, which was aggravated by the radiation sickness consequent to the necessary irradiation of large body areas General supportive therapy was given concomitantly with the irradiation, and frequent transfusions were administered. A leukopenia also developed which was difficult to control

In one patient an effort at palliation was made by the use of radioactive phosphorus which resulted in a regression in the size of the tumor and improved control of bowel movements (which had been completely lost) but without improvement in bladder control (which was also suffering from neurogenic disability) The patient succumbed 26 months after the onset of treatment.

Another patient received nitrogen mustard therapy She was given 1.5 mg daily for a period of five days, from which she derived good palliation in that she experienced constitutional improvement and a decrease in the size of the tumor She remained well for approximately one month after the completion of her first course of nitrogen mustard and was given a second course consisting of two injections of 1.5 mg and one injection of 3 mg. of the compound. She tolerated the nitrogen mustard well. It is hoped that additional experience with nitrogen mustard, or one of its derivatives in combination with irradiation may prove efficacious as a therapeutic modality

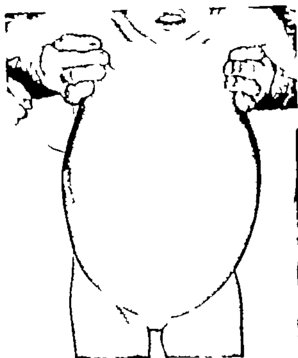


Fig 417 Neuroblastoma which practically fills the entire abdomen.

A third patient received a course of Coley's toxin which had no appreciable effect upon the size of the tumor but did apparently produce a good general response with symptomatic improvement. The response, however was transient, and the patient succumbed ten months after the onset of treatment.

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TUMORS OF PARAGANGLIONIC CELLS (PARAGANGLIOMAS)

INTRODUCTION

DEFINITION AND NOMENCLATURE

During the embryologic development of the nervous system a group of primitive cells migrate to the dorsal surface of the sympathetic ganglia and form small masses in depressions of these ganglia and are, therefore called *paraganglionic cells* Many of the paraganglionic cells of the sympathetic nervous system contain chromaffin granules and are engaged in the production of epinephrine. They reduce chromates which reaction is termed the "pheochrome" reaction. The paraganglionic cells can be found anywhere in the peripheral nervous system A group of these cells associated with the sympathetic nervous system, are found in the chain of ganglia extending from the base of the skull to the coccyx. Some cells especially those in the adrenal medulla to a lesser extent

in the retroperitoneal region, and occasionally in the posterior mediastinum, contain the above-described granules and are hormonally active. Many of the paraganglionic cells associated with the sympathetic nervous system and all those of the parasympathetic system are hormonally inactive.

Tumors, theoretically, can arise from the paraganglionic cells situated anywhere within the peripheral nervous system. The term *paraganglioma* designates the cell of origin. The tendency to name tumors of the paraganglionic cells because they are pheochrome positive, has led to the use of such terms as *pheochromocytoma* and *chromaffinoma*, and those, especially in the gastrointestinal tract, which have in addition the propensity of reacting to silver stains, are termed *argentaffinomas*. Certain tumors of the parasympathetic system have been called *paragangliomas* whereas others are merely given the nondescript term *tumor* with the tissue of origin as a prefix (*e.g.*, carotid-body tumor, glomus-jugulare tumor). Stout describes beautifully the ill-advised attempts of some to limit the term *paraganglioma* exclusively to hormonally active tumors.

The rejection of the term paraganglioma for these hormonally inactive tumors is based upon the desire of certain other students of the subject to reserve the names paraganglionic cells and paraganglionic tumors for those which are hormonally active. Since hormonally active cells are not found in the above-mentioned sites, these writers prefer to reject or ignore the probable common embryological origin of both cell types, and consign these hormonally inactive cells, and the tumors derived from them, to the limbo of bastards of undetermined parentage and without name, except for that of the locality in which they are found.

Tumors of the paraganglionic cells of the parasympathetic system which present similar clinical syndromes are those arising from the carotid body, the ganglion nodosum of the vagus nerve, the ganglia of the ninth cranial nerve within the middle ear, ciliary ganglia, and possibly from the aortic bodies, the organ of Zuckerkandl.

All paragangliomas resemble each other morphologically, although the nonchromaffin ones are devoid of chromaffin granules. They are usually well encapsulated and rarely metastasize, although an occasional malignant paraganglioma may occur. They all have a tendency for continued growth after incomplete surgical excisions.

Paragangliomas which are hormonally active, the pheochromocytomas of the adrenal medulla and occasionally of the posterior mediastinum and retroperitoneal space, possess all morphologic characteristics of those paragangliomas which are hormonally inert. The latter are also located in the adrenal medulla, and on occasion both cell types may be present (those which contain the granules that are pheochrome positive and those which do not produce the hormones). Both types are usually benign morphologically, although malignant variants may occur.

Paragangliomas are treated exclusively by surgical extirpation. The tumors are radioresistant, and irradiation, as a rule, can offer very little for their control.

The treatment of the individual paragangliomas present specific problems inherent to their location and metabolic activity.

PARAGANGLIOMAS OF THE CAROTID BODY AND RELATED STRUCTURES

The exact anatomic classification of the carotid body and certain related structures has not been completely determined. Some claim they should be grouped with the paragangliomatous tissue throughout the body (including the adrenal gland), others, especially Lattes, advise separating the group into

a distinct subdivision termed the *non chromaffin paraganglion cells* while other students attribute a mesodermal origin to this group of epithelial cells

Lattes has divided the tissues under discussion into four broad categories, believing that they are homologous parts of the same system and he has grouped all of these various structures in different classes based on his interpretation of their morphologic and functional significance His classification is as follows

1 The neuromyoarterial glomus, which is an arteriovenous anastomosis. Examples are the typical glomus structure in the tips of the fingers and toes and the glomus coccygeum

2. The carotid and aortic sinus Special sensory nerve endings occurring in a circumscribed fashion within the walls of the internal carotid artery and aortic arch the pressoreceptors sensitive to stimulation occurring through variations of pressure within the carotid and aortic arteries

3 Chromaffin tissue or paraganglia of the conventional type, notably the adrenal medulla, and the chromaffin cells occurring within the visceral sympathetic ganglia in the thoracolumbar chain and in the celiac and pelvic plexuses Lattes includes the following criteria to distinguish this class (a) secretion of epinephrine or similar substance, (b) a positive chromaffin reaction (c) efferent motor sympathetic innervation and (d) common embryologic origin with the ganglion cells of the sympathetic nervous system

4. The nonchromaffin paraganglia, in which group Lattes includes the true carotid body the glomus jugulare, and the paraganglion tympanicum the paraganglion intravagale and juxtavagale the aortic arch bodies or glomus aorticum or cardioaortic bodies and the paraganglion ciliare (described only in monkeys) Lattes states that the following criteria are necessary for inclusion in this group (a) associated in their development with vessels of the embryonic branchial arches and the cranial nerves (b) histologically similar to each other because of their peculiar epithelioid cells with vascular stroma (c) they are provided with an afferent sensory type of innervation from fibers that are probably parasympathetic or different cranial nerves (d) probably no chromaffin substance present (e) no epinephrine or other detectable hormone is secreted (f) the presumptive function is said to be that of chemoreceptors capable of noting changes in the hydrogen ion or carbon dioxide concentration in the blood and (g) tumors originating from these bodies have similar histologic structure and behavior and have a tendency to be multicentric in origin

In the following discussion the nonchromaffin paragangliomas will be presented, after which tumors of the chromaffin paraganglion system (pheochromocytomas) will be discussed.

The nonchromaffin paragangliomas of the cervical region include neoplasms arising in the carotid body the aortic bodies, glomus jugulare and paraganglion structures associated with the ganglion nodosum of the vagus nerve.

Carotid-body paragangliomas are by far the most frequent, hence will be discussed in detail.

CAROTID BODY PARAGANGLIOMA*

The carotid body paraganglioma is a slowly growing painless firm tumor situated usually within the bifurcation of the common carotid artery with lateral but not vertical mobility, with transmitted but not expansile pulsation with diminution in size following carotid

* In collaboration with Theodore R. Miller and Fernando Gentil.



Fig 418 Coronal section (from behind) of the aorta and the origin of the innominate artery in a 23 mm human embryo The "paraganglionic" condensations related to the lateral aspect of the innominate artery (*i a*) and to the upper surface of the ductus arteriosus (*d a*) are shown (*Courtesy*, Dr James D Boyd)



Fig 419 Transverse section of the internal carotid artery in a 30 mm human embryo to show connection at this stage between the sympathetic and the carotid body (*Courtesy*, Dr James D Boyd)

compression and a history of several years' duration

Von Haller is generally accredited with the first anatomic description of the carotid body in 1743, he designated it as *ganglion minutum* The first microscopic appearance of the structure of the carotid body was described in 1862, by Luschka, who called it *ganglion intercaroticum* Marchand is said to have first recognized the carotid-body tumor, and Riegner in 1880 probably was the first surgeon to remove the tumor, this operation required the ligation of the common carotid artery with resultant hemiplegia and death on the third postoperative day Maydl in 1886 published the first recorded survival after extirpation of this tumor, although his patient sustained a transient hemiplegia Middleton in 1897 was the first American surgeon to remove a tumor of the carotid body

EMBRYOLOGY OF THE CAROTID BODY

The carotid body is inconstantly found in man, Funke (1904) was able to demonstrate the carotid body in only one of eight fetuses dissected When present, the carotid bodies are found well developed in embryos of 10 weeks' gestation

The exact origin of the carotid body remains uncertain, numerous theories have been advanced to explain its development from such structures as (a) the pharyngeal entoderm, (b) the mesoderm of the third branchial arch (Maurer), (c) the adventitia of the first part of the internal carotid artery, (d) the cervical sympathetic trunk, and (e) cells originating from the glossopharyngeal and vagal ganglia

In his classic treatise on the development of the human carotid body, James

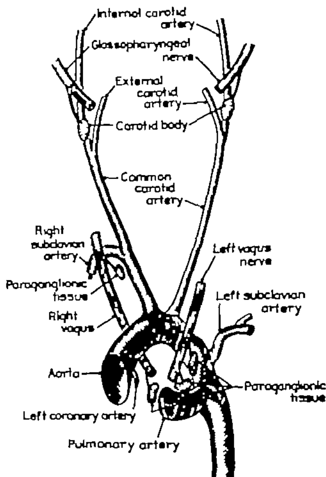


FIG. 420 Illustrating the paraganglionic structures of the upper thorax and neck. (*Courtesy* Dr James D Boyd.)

Dixon Boyd refers to this structure as a *paraganglion*, meaning a structure of which the essential cells are derived in their entirety from the nervous system. He assumes they have the same genetic origin as the precursors of the true gan glionic cells, but in the paraganglia the primitive cells instead of undergoing the function of differentiation, develop into structures having the appearance at least of a secretory function.

In Fig. 418 which is a reconstruction of the main arterial trunk in a 23 mm human embryo Boyd has shown the possible locations of the paraganglia.

When such paraganglia are demon strated, one may occur near the innomi nate artery usually on its lateral aspect and supplied by fibers of the right vagus nerve The same body occasionally may be closer to the bifurcation of the in nominate artery or lateral to the right subclavian artery A second paragan-glion is situated on the anterolateral as pect of the left side of the aortic arch and is supplied by the left vagus nerve. A third paraganglion is located just above the ductus arteriosus in the angle between this vessel and the descending segment of the aortic arch. A fourth paraganglion is located on the right side and upper surface of the trunk of the pulmonary artery and is related on its right side to the ascending aorta and the left coronary artery As will be shown later it is possible for tumors of the carotid body type (paragangliomas) to develop in any of the paraganglia.

ANATOMY OF THE CAROTID BODY

The carotid body has been variously designated as *carotid body nodulus caroticus glandula carotica glomerulus arteriosus glandula intercarotica para ganglion intercaroticum, ganglion inter*

caroticum, ganglion minimum, and *ganglion exiguum*

The carotid body is the largest of the paraganglia in the nonchromaffin system, the normal body measures about 2 to 5 mm in size, which corresponds to a hemp seed or a grain of rice The carotid body is ovoid in shape as a rule and yellowish pink in color It is supplied by the vagus nerve, the hypoglossal nerve, the superior cervical sympathetic ganglion, and the descending branch of the glossopharyngeal nerve, which also gives origin to the carotid sinus nerve of Hering The carotid body in its location within the carotid bifurcation is united to the major vessels by a firm connective-tissue band which is called the ligament of Mayer. The thin capsule surrounding the carotid body has prolongations or projections of its fibers extending inward to form septa which divide the groups of parenchymal cells into lobules or "cell balls" The blood supply of the carotid body, which reaches it through this fibrovascular ligament of Mayer, is usually the first small arterial branch which leaves the main stem of the external carotid artery to enter the lower pole of the carotid body, where it branches through the fibrous septa together with the medullated and nonmedullated nerve fibers to ramify and form a very definite capillary network around the bodies of cells The previously mentioned nerve fibers enter the cell nests and break up into small tendrils with buttonlike ends

The main cells of the carotid body proper are large, pale, polygonal cells with finely granular cytoplasm and vacuolated nuclei Plasma cells may occasionally be demonstrated

PHYSIOLOGY OF THE CAROTID BODY

One might logically concur that the carotid bodies have no important function inasmuch as they can be removed in children without any unusual or significant signs

In a series of studies on dogs, Schmidt and Comroe came to the conclusion that the major function of the carotid bodies was due to the presence within them of chemoreceptors which respond to chemical changes, notably the oxygen tension of the blood, in a similar manner to the way in which the respiratory center responds to changes in the carbon dioxide tension Through these nerve endings, which are chemoreceptors, reflex changes in respiration are said to be presumably effected. However, Lewison and Weinberg deny this theory and affirm that no evidence exists to indicate that the carotid body is an endocrine gland with any detectable internal secretion They illustrate this point of view by a case report in which complete removal of bilateral carotid-body tumors did not produce any noticeable alterations in the respiratory or circulatory functions They warn the physician not to confuse the supposed function of the carotid body with the functions of the carotid sinus, which are well known to be important in controlling blood pressure

PATHOLOGIC ANATOMY OF CAROTID-BODY TUMORS

We are indebted to Malcolm Dockerty for clarification of the patterns into which tumors of the carotid body fall He has classified these tumors into two characteristic groups which may be seen alone or in mixed form

The alveolar or insular pattern In this type of carotid body tumor, the pale, polyhedral cells are distributed in large islands separated by thin-walled fibrous septa. The lobules of tumor cells are surrounded by large, thin-walled vascular sinuses He describes a thin mantle of epithelial cells intervening between the tumor buds and the vascular lumens

The peritheliomatous pattern In this

group Dockerty describes the cellular units as smaller irregular and composed of groups of cells arranged in irregular strands and separated by vascular connective tissue. The cells surround the vascular sinuses, which are abundant. The nuclei are oval in shape and eccentric in position. There is considerable hyalinization of the connective tissue

Is the Carotid-body Tumor Ever Malignant?

The carotid body tumor is generally considered to be a benign neoplasm, which consideration is based on the infrequency of metastases to lymph nodes and viscera in any reported *series of cases Instances have been recorded,* however of metastases to the ovary and liver In a review of ten such tumors William S MacComb classified five as benign and five as malignant, the criteria of malignancy were infiltration of the capsule by the tumor and invasion of the lymphatic vessels

Bilaterality and Heredity of Carotid-body Tumors

That there is a familial incidence of this tumor is an acknowledged possibility inasmuch as several instances have been reported wherein siblings had similar tumors Bilateral carotid body tumors are rare, but do occur Lewison and Weinberg reported bilateral carotid body tumors occurring simultaneously and coupled with three verified unilateral tumors developing in three first cousins

CLINICAL FEATURES

Incidence, Age, and Sex Distribution of Carotid-body Tumors

With the exception of tumors of the parathyroid glands the carotid body tumors are the rarest of all cervical neoplasms The ratio of 3 males to 2 females is generally found to exist in any selected series of cases Although the average age of the patients in MacComb's *series* was 38 years, *the tumors* have been observed in children

Symptomatology

The most important single fact about the symptomatology of carotid body tumors *is* that *they are usually painless* The symptoms may be due to pressure phenomena such as (a) pressure on the vagus nerve, (b) pressure on the recurrent laryngeal nerve producing hoarseness and cough, and (c) pressure on the tonsil, pharynx, and esophagus, *producing dysphagia.* Bulging of the pharyngeal wall may be seen The patient may complain of headache, dyspnea, hoarseness dysphagia, cough, and tinnitus aurium. Dilation or contraction of the pupil has been seen in fact, the typical Horner's syndrome may *develop* The Adams-Stokes syndrome may occur The unusual carotid sinus syndrome may be produced by either one of two mechanisms—direct pressure or reflex arc—but does not occur in every case, in fact, it seems to be an infrequent association which is surprising *in view of the location of the tumor* Each one of the three types of carotid sinus syndromes as reported by Redeon and Dumee has occurred (1) the cardioinhibitory type characterized by a slow pulse with or without hypotension, (2) the vasodepressor type in which there is a fall of blood pressure with cerebral anemia, and (3) the cerebral type in which the syncope is not accompanied by any modifications in the pulse or the blood pressure.

Rate of Growth

One of the pathognomonic features of carotid body tumors is their noto-

riously slow rate of growth, often over many years. Goldberg observed that the average duration of the carotid-body tumor before the patient visited a physician was seven years He reported the instances of nine tumors removed after an average duration of 20 years. The slow rate of asymptomatic growth was apparently responsible for the lack of concern by the patient and the procrastination before treatment

Physical Signs

The common physical sign of a carotid-body tumor is the presence of a single neoplasm, ovoid and rounded in shape, smooth, firm, and elastic, nonfluctuant in character, not attached to the skin, and deeply situated in the upper cervical triangle at the bifurcation of the common carotid artery The tumor is movable laterally but not vertically because it rests in the crotch of the carotid bifurcation It is occasionally wedged tightly between the mandible and the mastoid process and inferiorly may extend downward as far as the clavicle There may be a transmitted but not an expansile pulsation which is sometimes difficult to distinguish from the expansile pulsation of a carotid aneurysm At times a bruit or thrill can be elicited

DIAGNOSIS

In general the diagnosis is not commonly made preoperatively because of the rarity of the tumor and the average surgeon's limited experience The differential diagnosis must include a consideration of aneurysm of the carotid artery, metastatic cancer involving a cervical lymph node, aberrant thyroid and thyroid tumors, branchiogenic cysts, and neuromas of the phrenic and vagus nerves

Aspiration biopsy has been done, using a 17-gauge aspirating needle under negative suction, and the tissue so obtained has at times been diagnostic, but the histogenesis is not so readily determinable as in the case of metastatic tumors involving cervical lymph nodes, the chief value of aspiration biopsy, therefore, is in differential diagnosis, the recognition of other tumors that might be mistaken for carotid-body tumor

Compression of the common carotid artery below the level of the tumor abolishes the pulsation, the bruit, and the thrill, and sometimes diminishes the size of the tumor

The criteria, therefore, on which the diagnosis of carotid-body tumors is generally made depend on these well-known symptoms and signs (a) a slowly growing, painless, firm, deeply situated tumor in the region of the bifurcation of the common carotid artery, (b) a history of many months or even years of slow, asymptomatic growth, (c) mobility in the lateral direction, but very limited vertical mobility, due to its position in the crotch of the carotid bifurcation, (d) a transmitted but not expansile pulsation, and (e) a diminution in size by compression of the common carotid artery proximal to or below the tumor

TREATMENT OF CAROTID-BODY PARAGANGLIOMAS

Inasmuch as tumors of the carotid body are notoriously resistant to x-ray and radium therapy, the only treatment possible is surgical extirpation Although surgeons experience the normal compulsion of removing any neoplasm once identified and diagnosed, decision in this instance must rest on the surgeon's evaluation of the dangers involved, i e, whether the persistent tumor in the years to come is more dangerous than the risk of removing it We have previously stated that the tumor is essentially a benign neoplasm if one considers its rate and manner of growth, the qualifications of malignancy resting

more or less on occasional invasion and direct growth into the lumina of the large adjacent vessels Hayes Martin, for example, pursues the policy of non surgical intervention if the tumor is not readily resectable, he concludes that it is preferable to leave the tumor alone because it is seldom fatal as the result of its slow continued growth. The weighty problem which confronts the therapist is not how to remove the tumor but whether it should be removed or not.

In the event that surgical excision is attempted, a generous, long incision should be made bordering the anterior margin of the sternocleidomastoid muscle The platysma muscle is severed and the skin flaps are widely elevated. The deep fascia is similarly incised and the sternomastoid muscle is retracted posteriorly It is a wise precaution to start the operation by immediately isolating the common carotid artery in the base of the neck and placing a narrow strand of umbilical tape around the artery this tape is not tied but is in place to function as a precaution in the event that the more distal artery which is closely approximated if not incorporated in the tumor is lacerated in the course of the operation The internal jugular vein, which is so frequently attenuated across the surface of the tumor is divided and ligated so that it will not interfere in the subsequent operation The vagus and sympathetic nerves are dissected free and preserved, as are the hypoglossal nerve and the superior laryngeal nerve if possible, because some of the most unpleasant sequelae of excision of a carotid body tumor is an injury to these nerves and the consequent complication of paralysis

Hazards of Carotid Artery Ligation

Inasmuch as the fatalities associated with carotid body tumors result usually from attempts at removal of the tumor every precaution should be exercised in order to lessen the hazards of vascular injury which is the chief cause of death Because the tumor is so intimately adherent to or incorporated in the bifurcation of the carotid artery it is almost technically impossible to remove the neoplasm in its entirety in the majority of cases without at the same time sacrificing a segment of the common carotid or internal carotid arteries Accidental hemorrhage through laceration of the vessel made fragile by tumor infiltration may sometimes force the hand of the surgeon in ligating and subsequently excising a segment of these arteries.

Surgeons have long attempted modifications of operative technic or the development of mechanical devices designed for the gradual occlusion of the common carotid artery in the hope that with the lapse of time an adequate collateral circulation may be expanded to take care of the needs of the terminal arterial supply and prevent the hazards of cerebral thrombosis, brain injury hemiplegia and death. In 1901 George Crile designed a screw clamp with a spring which was applied gradually in the course of twenty four hours and could be released if symptoms of cerebral damage appeared during this interval of gradual arterial occlusion In 1906 Halsted utilized small bands of aluminum to secure gradual occlusion of the artery and Rudolph Matas in 1911 employed the same principle but preferred strips of fascia lata

Matas suggested the following prophylactic measure The common carotid artery should be systematically compressed against the large anterior tubercle of the transverse process of the sixth cervical vertebra several times a day with longer daily periods on consecutive days for a few weeks on the principle that the collateral circulation to the brain on the affected side would be gradually increased sufficiently to take care of the blood supply and survival of these tissues when the carotid

artery is completely and permanently ligated The patient himself is taught to do this compression Certainly, if the patient cannot tolerate the external compression of the carotid artery by this technic, then a surgical occlusion of the common or internal carotid arteries should not be done

Syncope may occur just during manipulation of the tumor and during its removal, particularly if the operation is being attempted under local anesthesia Procaine solution may be used to infiltrate in the adventitia in order to block the nerve receptors in the carotid sinus, although this is not always technically possible

Lambert Rogers in 1944 suggested the use of electroencephalograms after compression of the common carotid artery for thirty to sixty minutes as a helpful indication of the competence of the collateral circulation, although this is a helpful guide to the surgeon, it does not afford assurance that delayed hemiplegia may not subsequently occur However, if the electroencephalographic demonstration during the course of the surgical resection shows that the collateral circulation is so deficient as to promise brain damage, then the operation should be terminated if the carotid-body tumor itself is inseparably fused with the carotid vessels

The hazards of cerebral damage are greater if the internal and external carotid arteries are ligated than if the common carotid alone is tied But the former must necessarily be done in many of the cases because of the high situation of the carotid body tumor in the carotid bifurcation The conditions under which carotid ligation occurs, therefore, in the instance of a carotid-body tumor, are not the same as in the case of wounds of the common carotid artery, in fact, they are more hazardous

The collateral circulation following ligation of the common carotid artery is established between the carotid arteries of the opposite side, both intra- and extracranially The subclavian artery on the side of ligation invariably enlarges in time, with expansion as well of the other arterial tributaries which it supplies to the head and neck The superior and inferior labial arteries, the angular arteries and the frontal branches of the superficial temporal arteries form anastomoses across the face and aid somewhat in this collateral circulation through the external carotid artery The chief reliance, however, is upon the vertebral artery, which is the main source of intracranial collateral circulation If the external carotid artery is not tied, a retrograde flow by way of the branches of the external carotid artery occurs The vertebral artery should reinforce somewhat the blood supply through the circle of Willis, but this is not always adequate and cannot be relied on with certainty The younger the patient, of course, the better the chance for survival after ligation of the common or internal carotid arteries The hemiplegia which occurs may be permanent or transitory It may occur immediately after the operation or even during this procedure when the carotid artery is ligated if there is deficient collateral circulation to the cerebral hemisphere, particularly in older individuals, or the hemiplegia may not occur for twenty-four to forty-eight hours, in which event the cause may be due to ascending thrombosis which ultimately occludes the middle cerebral artery The thrombosis in the internal carotid artery has been attributed to trauma of the intimal layer of the vessel brought about by the ligation Dandy has urged the prevention of this injury by the prophylactic interposition of a strip of fascia lata between the ligature and the walls of the artery

Other postoperative aids to prevent possible thrombosis have been suggested, such as the heparinization of the patient A second measure has been

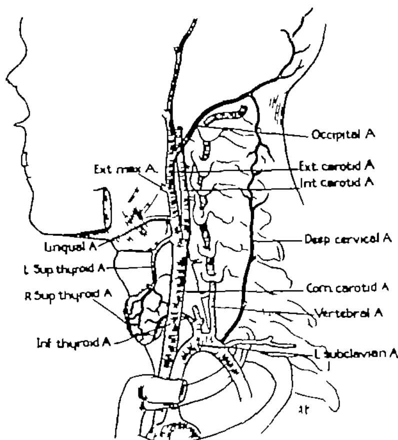


FIG. 421 Anastomotic arterial network in the neck. (*Courtesy* Watson and Silverstone and Ann. Surg. *109*:12, 1939)

suggested by Schornstein (1940) by which after ligation of the common carotid artery the patient is placed in a Trendelenburg position for ten days and then is not allowed up for another two or three weeks, the intention being to lessen the danger of hemiplegia.

ANASTOMOTIC PROCEDURE TO LESSEN HAZARDS OF CAROTID LIGATION*

A technic of resecting the entire carotid complex (common carotid artery internal carotid artery and external carotid artery) has been developed by Conley and Pack for those patients on whom carotid artery resection is absolutely necessary They have found by experiments on dogs and trials on human beings that the simple expedient of anastomosing the distal ends of the severed external and internal carotid arteries will permit a continuous flow of blood through this terminal sufficient to prevent arterial thrombosis, hemiplegia, and death

Vascular transplants of autogenous veins or homologous arteries would solve the problem of maintaining the blood supply to the brain were it not for the frequent handicaps of infection, radiation necrosis and damage, poor tissue bed, and unavailability of suitable grafts It is well known that the external carotid artery has such large anastomotic communications with other arteries in its terminal distribution that retrograde hemorrhage from its distal severed end can be rapid and great.

In the belief that even a slight flow of blood through the internal carotid artery would prevent the dangerous thrombosis and perhaps preserve the integrity of the brain, it was planned to anastomose the distal severed ends of the internal and external carotid arteries on the same side of the neck after excision of the carotid bulb (Fig 421)

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* In collaboration with John J Conley

The principle of anastomosing two end arteries, both severed from their proximal and main blood supply, would appear unorthodox, were it not for the known possibility of reversal of blood flow, especially from the external carotid artery

This technic of anastomosing the cut ends of the internal and external carotid arteries high in the neck was developed in the hope of salvaging some patients who would otherwise die of cancer and fatal carotid arterial hemorrhage This anastomosis permits the blood to flow through the anastomotic connections of the external carotid artery from the contralateral side into the external carotid artery of the ipsilateral side and thence into the internal carotid artery and circle of Willis, in all instances wherein the arterial blood pressure in the ipsilateral internal carotid artery is less than that in the ipsilateral external carotid artery The blood pressure in the ipsilateral internal carotid artery is not always, or necessarily, lower than that in the corresponding external carotid artery However, when it is lower, communication with the opposite arterial supply through the anastomotic network of the face and neck may mean the difference between life and death When the pressure in the ipsilateral internal carotid is greater than the pressure in the corresponding external carotid artery, the direction of blood flow after the anastomosis is completed would be from the brain into the internal carotid and external carotid arteries and then into the face and neck This situation would indicate that in such an instance the efficiency of the circle of Willis is more effective than that of the anastomotic bed of the face and neck

The desirability of having a continuous arterial channel for the flow of blood in either direction, which is accomplished by the anastomosis, is self-evident The anastomosis has definite advantages over the dead-end which exists when the internal carotid artery is ligated The free movement of blood in itself means additional nourishment to the brain through the medium of the anastomosis The free movement of arterial blood has another great advantage in that the predisposition to thrombus formation in the artery is markedly diminished Thrombus formation following ligations of the internal carotid and even the common artery have been frequently recorded as a cause of death by the propagation of this thrombus into the middle cerebral artery

Technic of External and Internal Carotid-artery Anastomosis

The specific technic of the anastomosis of the internal carotid artery to the external carotid artery is governed somewhat by the local conditions necessitating this procedure In postoperative slough of the neck following intensive unsuccessful irradiation or in primary postirradiation slough of the neck, the carotid vessels are usually readily accessible from a surgical point of view It is important to remove all portions of the carotid arteries whose integrity has been jeopardized by the irradiation or in the sloughing process so that the anastomosis will have a favorable opportunity for healing In very extensive cancers of the neck involving not only the jugular vein but the carotid artery, the dissection is much more involved because of the usual inaccessibility of the arteries for anastomosis and the advisability of removing the entire lateral neck contents, including the great vascular channels, in continuity This feat is accomplished by the liberation of the trapezius muscle forward toward the carotid complex The common carotid artery may be ligated along with the internal jugular vein at the beginning of this procedure The preparation for the ligation of the internal and external

carotid arteries should be synchronized with the plans for immediate anastomosis of the stumps of these two vessels In order to shorten the time elapsing between the excision and anastomosis, the superior limits of the external and internal carotid arteries are liberated and made accessible before the lateral compartments of the neck are removed.

In the case of carotid body tumors the great vessels are readily accessible and the opportunities for anastomosis are usually not encumbered

Whenever possible, intraarterial pressure tests should be performed upon the various carotid arteries before and after the completion of the ligation and excision. Sweet's sensitive manometer is most satisfactory in securing these readings during the operation. When excision of the carotid bulb is anticipated, the patient should be studied preoperatively by angiography of the circle of Willis in order to ascertain any variations or anomalies in the size of the constituent arteries. Electroencephalograms should be taken before the operation, during the procedure of ligation and anastomosis, and in the postoperative period.

The time required for the actual anastomosis is seldom more than five to ten minutes. The superior cervical ganglion is first injected with 1 per cent procaine to lessen the hazard of cerebral angiospasm. The carotid sinus is then anesthetized by the injection of 1 per cent procaine to avoid the carotid sinus syndrome Appropriate arterial clamps are then placed across the inferior segment of the common carotid artery and other arterial clamps are then placed at appropriate positions on the internal and external carotid arteries The latter two clamps are placed on the vessels in a vertical position, so that when the arteries are cut and the clamps rotated the most medial aspect of the vessel wall will become accessible for suturing The vessels are severed about 4 mm. beneath the level of the artery clamps and the anastomosis is then accomplished by interrupted everting mattress sutures Only a few of these mattress sutures of #0000 silk on atraumatic needles are necessary to approximate the cut ends of the arteries depending, of course on the diameter of the lumina. If one of the carotid arteries is larger in diameter than the other this disproportion may be overcome by cutting the artery with the small diameter in an oblique manner thus increasing its over-all circumference.

As soon as the anastomosis has been completed the clamps are released and blood will flow through the new arterial junction with considerable pressure. Pulsations are immediately felt in both vessels There may be a tendency toward acute angulation or kinking at the site of the anastomosis thus diminishing the effectiveness of the repair This is overcome by an elevating suture through the wall of the vessel posteriorly and then through the deep muscles of the neck at a higher level, in order to cause a more graceful curvature of the anastomosed vessels. Any tests or measurements of intraarterial pressures on the cut vessels may be ascertained at this time by appropriate instrumentation. The stump of the common carotid artery is doubly transfixed with #00 silk and pulled out of its normal position in the neck to the posterior part of the lower neck flap in the region of the trapezius muscle by a through-and through stitch in the skin. This removes the artery from the line of incision and also from any possibility of contamination by mouth or by pharyngeal or esophageal secretions, if a fistula into this region exists or should develop The anastomosis is then covered with the previously prepared skin flaps, or in the event that it was necessary to excise the skin, a free graft may be placed over the arteries.

Atheromatous plaques involving the

walls of the carotid-artery complex are common in the age group over 50 years, in fact, atheromatous plaques seem to have a predilection for the region of the carotid bulb Occasionally, this plaque will extend inferiorly into the common carotid artery and superiorly into the internal carotid artery If careful palpation and inspection of the arterial wall indicate that a large atheromatous plaque is contained therein, the anastomosis should be accomplished beyond the limits of this condition If the atheroma extends inferiorly into the common carotid artery, ligation with silk may cause the vessel to rupture, with severe hemorrhage Dandy has recommended that the vessel be ligated with fascia lata or that a cuff of fascia lata be placed about the vessel if ligation with silk or wire is anticipated

RECURRENCE OF CAROTID-BODY TUMORS

Recurrence following surgical excision of carotid-body tumors has been notoriously great because many surgeons, including the writers, have in the past removed only the bulk of the tumor and permitted a rim of it to remain attached to the essential vessels Now that blood-vessel grafts are being more commonly used, the procedure of choice would be an excision of the common carotid and internal carotid arteries inferior and superior to the carotid-body tumors, with ligation of the external carotid artery and the insertion of a blood-vessel graft in the defect A homologous graft from a human is inserted, the intima is ultimately replaced by the growth of new intima from each end of the individual's arteries, but if a vein graft is substituted with external support by encasement of fascia or peritoneum, the same intima is retained and the vein wall, although subject to undue stress, may ultimately become thicker and more resistant to intrinsic pressure

END RESULTS IN THE TREATMENT OF CAROTID-BODY TUMORS

Phelps, Case, and Snyder collected a series of cases and established the average operative mortality to be 24 per cent, the operative deaths occurred in those patients in whom the common or internal carotid arteries were ligated William MacComb, in reporting ten cases from the Memorial Cancer Center, found that only three of the patients had the carotid-body tumor removed without injury to these essential arteries In the other seven cases the common carotid and internal carotid arteries were ligated, four of these seven patients had hemiplegia and died postoperatively The operative mortality, therefore, in the Memorial Hospital series was 58 per cent of those patients having ligations of the common and internal carotid arteries Watson, also from the Memorial Cancer Center, reported his end results following twenty ligations of the common carotid artery during the period 1926 to 1937 These ligations, however, were for other causes than incidental to the removal of the carotid body tumors Eleven patients (55 per cent) died within five days after the operation whereas nine (45 per cent) recovered immediately Of the nine who recovered, or rather survived, the immediate operative hazards, two patients died subsequently, one 2½ and one 3 months postoperatively, presumably due to late thrombosis

CASE REPORT NO 73 CAROTID-BODY TUMOR (PARAGANGLIOMA)

B P , a 31-year-old man, had been aware for 10 years of the presence of a mass in the right upper neck For nine years the growth of the tumor had been slow and uneventful without provoking symptoms For one year

he had experienced a choking sensation in his throat and had observed some weakness of the facial muscles on the right side.

On examination, a mass measuring 5 cm in diameter was situated in the region of the right carotid bulb The mass was firm in consistency movable transversely but not vertically Except for slight facial hemiatrophy there were no neurologic changes apparent.

The presumptive diagnosis was right carotid body tumor Under intratracheal anesthesia the tumor was dissected free of the upper cervical structures with the exception of the carotid bulb The internal jugular vein was resected and the vagus nerve was carefully freed from the lateral aspects of the tumor The neoplasm was densely adherent and formed part of the wall of the external and internal carotid arteries at the bifurcation In the dissection a thin wall of tumor was left in situ and no attempt was made to resect the internal carotid artery

The postoperative course was complicated by temporary weakness of the face the right vocal cord, and the right side of the tongue due to traction injuries to the vagus, facial and hypoglossal nerves but these completely improved without residual paralysis. Four years later there was still a residual palpable tumor overlying the carotid bulb but it was of minimal size and apparently inactive The residual tumor grew and a second operation was planned. The carotid body tumor together with the infiltrated carotid bifurcation was surgically excised. The common carotid artery was ligated The distal end arteries and the external and internal carotid arteries were united by end to-end anastomosis There was sufficient circulation retrograde to keep the arterial circuit open Convalescence was uneventful there were no complications

GLOMUS JUGULARE TUMOR (PARAGANGLIOMA)

Guild in 1941 first described a structure within the temporal bone which he termed the *glomus jugularis* It is located just beneath the bony floor of the middle ear in the adventitia of the dome of the jugular bulb closely associated with the tympanic branch of the glossopharyngeal nerve. It is morphologically similar to the carotid body is innervated by the glossopharyngeal nerve and receives its vascular supply through the inferior tympanic branch of the ascending pharyngeal artery (as does the carotid body) He therefore believed that this was a structure of a similar nature to the carotid body Its exact function is not known Similar structures arise in various locations associated with the tympanic nerve and are called paraganglia tympanica. LeCompt believes that this group should be presented as one.

The first tumor arising from the glomus jugulare was described by Rosenwasser after the pathologic diagnosis had been made by Otani in 1945 Since then about 18 cases have been reported in the literature, and Winship Klopp and Jenkins list 13 probable cases It is believed that many of the hemangiomas endotheliomas and hemangioendotheliomas of the middle ear previously reported may in reality have been instances of nonchromaffin paragangliomas of the glomus jugulare

The tumors usually occur in the fifth decennium but have been reported in a 5-year-old child and a 78-year-old male. Women are somewhat more frequently afflicted. The symptoms as described by Winship *et al.* are a long history of (1) an aural polyp (2) profuse bleeding and recurrence after traumatization or attempts at local excision (3) progressive loss of hearing, (4) chronic otorrhea, (5) a subjective sense of pounding noise and pulsation in the ear synchronous with the arterial pulse (Lattes and Waltner) and (6) facial paralysis and pain in more severe cases

Physical examination will reveal a polypoid soft, purplish mass arising in the middle ear and usually extending in the external ear It extends to con

tiguous structures, frequently invading the temporal bone, and with continued growth may erode into the cavity Most are benign, although two reported by Lattes and one by Winship *et al* were malignant and produced metastases

In the differential diagnosis many of these tumors have been mistakenly treated for either mastoiditis, cholesteatoma, or aural polyp

TREATMENT

The treatment is exclusively surgical, preferably by a radical mastoidectomy Some symptomatic response has been described following irradiation but no cures have been reported by the exclusive use of this modality Adequate data are not available to evaluate treatment methods, but, because of the anatomic inaccessibility of many of these tumors when diagnosed and their marked vascularity, it would appear that operative resection followed by either interstitial radon seeds or externally applied roentgen irradiation would be the preferred method for treating these tumors Profuse bleeding during operation due to the marked vascularity of these tumors may be minimized by a preliminary ligation of the ipsilateral external carotid artery

PARAGANGLIOMAS OF OTHER SITES

MISCELLANEOUS PARAGANGLIOMAS OF THE NECK

In addition to ganglioneuromas arising from the ganglionic cells, described previously, there have been three paragangliomas arising from the nonchromaffin paraganglionic cells closely associated with the nodose ganglion Stout reported one such tumor in 1935 in a 52-year-old woman, occurring within the vagal sheath and producing pharyngeal pressure This tumor was surgically resected and 16 years later was reported by Lattes as being asymptomatic An interesting feature is the presence microscopically of tumor cells within a large blood vessel Lattes presented two additional cases One of these was locally infiltrating and killed the patient by invading the cranium after an unsuccessful attempt at surgical extirpation The patient was found at autopsy to have another paraganglioma involving the opposite (left) carotid body A third most unusual case reported by Lattes revealed three separate paragangliomas, one arising in the vagus nerve in the region of the ganglion nodosa, another from the bifurcation of the carotid body, and another in the adventita of the aortic arch Lattes cites an unpublished paraganglioma of the vagus nerve observed by Mathews which extended up the base of the skull This tumor arising from the aortic arch, and another one arising from the innominate artery, are apparently the first tumors of aortic bodies to be reported in man, although Bloom in 1943 had reported their occurrence in dogs

The surgical considerations pertaining to the excision of ganglioneuromas of the vagal nodose ganglion discussed previously, apply similarly to the treatment of paragangliomas of this structure

No tumors in man have been reported arising from the ciliary paraganglionic cells, although they have been described in monkeys

INTRATHORACIC AND INTRAABDOMINAL PARAGANGLIOMAS

Nonchromaffin paragangliomas have been described arising within the thorax and abdomen Miller and Godwin each reported one arising from the posterior mediastinum A number have been recorded arising from the paravertebral

region of the abdomen, either from the adrenal or in the vicinity of the adrenal gland. One such instance was observed by the authors and, surprisingly it was a malignant paraganglioma. The exact classification of apparently nonfunctionary *adrenal tumors is difficult to ascertain* Some believe that all are functioning to a degree, being composed of pheochrome cells others believe that the malignant tumors have not generated the functional capacities of epinephrine or norepinephrine production and there are those who believe that the adrenal gland contains an admixture of cells nonchromaffin and those that are pheochrome positive. Each may produce tumors, the former nonfunctioning, the latter producing the classical syndrome of pheochromocytoma.

Nonfunctioning and functioning paragangliomas have been reported in the organ of Zuckerkandl. About 14 such neoplasms have been recorded. Handschin and Cahill reported multiple paragangliomas In the former report a 46-year-old male presented a paraganglioma of the organ of Zuckerkandl and a pheochromocytoma of the adrenal gland. In Cahill's patient there was present a large pheochromocytoma of the retroperitoneal region and a separate one at the bifurcation of the aorta. Pitega reports a malignant paraganglioma of the organ of Zuckerkandl which was unique in that it metastasized to the pancreas, renal cortex, and pleura. It was also physiologically functional, similar to pheochromocytoma. Only one other such instance of a malignant functional paraganglioma was reported, by Halscheidt. This was a tumor arising in the hilus of the left kidney in a 24-year-old male. Rosenthal and Willis have noted an association of these tumors with von Recklinghausen's disease

The occurrence of these neoplasms in regions other than the head and neck would serve to dispel the theory of Lattes concerning their mode of origin, that they are primarily concerned with some abnormality of the nervous tissue



FIG. 422. Intravenous pyelogram showing pressure effects upon the superior pole of the right kidney by a nonfunctioning retroperitoneal pheochromocytoma. (Case report No. 74.)



Fig 423 A retroperitoneal pheochromocytoma (Fig 422) which was independent of the adrenal gland and was nonfunctioning (Case report No 74)

cells associated with the embryologic evolution of human tissues from branchial-arch structure

CASE REPORT NO. 74. EXTRAADRENAL NONFUNCTIONING PARAGANGLIOMA

C C, a 64-year-old female, was admitted to the hospital complaining of pressure in the upper right quadrant with nausea and pain of 1 month's duration Two weeks prior to admission she developed a back pain on the right side in the lumbar region Occupying the right upper quadrant was a firm, fixed, nontender, ill-defined mass measuring approximately 10 × 12 cm Her blood pressure was 140/100 A gallbladder series, gastrointestinal series, and chest x-ray were all negative for evidence of pathologic involvement The intravenous pyelogram suggested the presence of a lesion involving the right kidney, and a retrograde pyelogram confirmed the fact that the right kidney was displaced downward by a mass which appeared to be extrinsic to the kidney, resulting in distortion of the internal architecture of that kidney The left kidney was normal Blood urea nitrogen was 16 mg per cent Blood hemoglobin equaled 14 gm per cent A tentative diagnosis of retroperitoneal sarcoma of undetermined histogenesis was made

During operative exploration through an oblique right loin incision, the kidney was found to be lower than normal, being displaced by a mass which was adherent to its posterior and medial aspect This mass was smooth, encapsulated, and reddish brown in color It measured approximately 12 × 10 cm It extended medially and was intimately adherent to the right renal pedicle and to the inferior vena cava and the aorta After careful and tedious dissection it was possible completely to free the tumor from

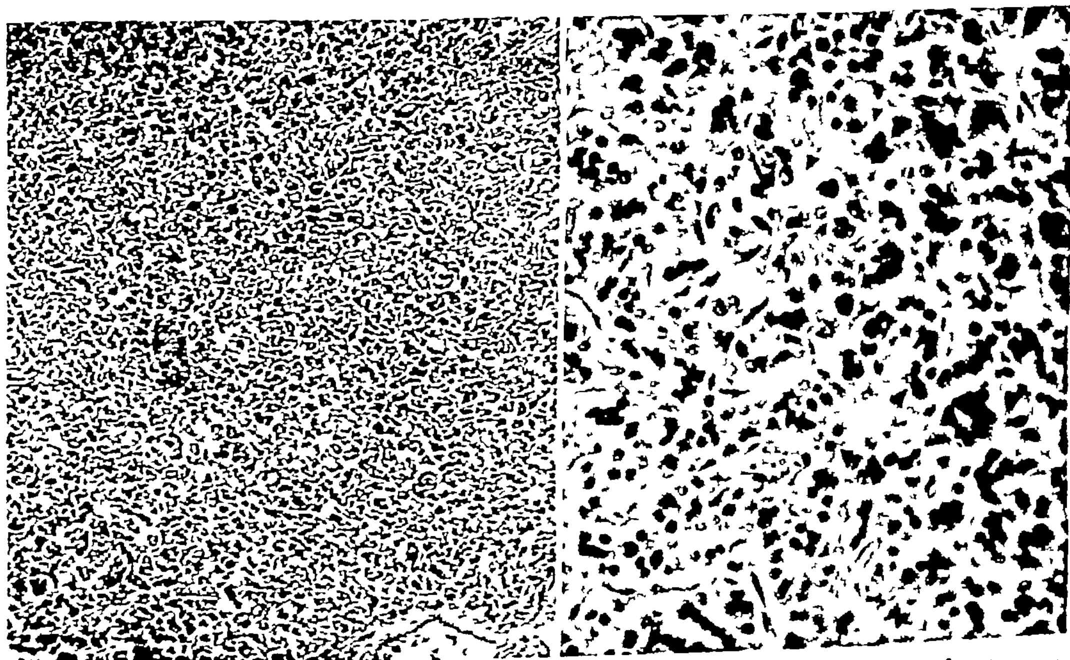


Fig 424 (*Left* and *right*) High- and low-power photomicrographs of retroperitoneal pheochromocytoma shown in Fig 423

the major vessels and it was removed together with the right kidney During the operative procedure the patient had an acute onset of cyanosis with marked rise in pulse rate to 160 and a drop in blood pressure to 90/70 due to an atelectasis of the left lung Immediately following bronchoscopy when a considerable amount of watery mucous secretion was aspirated from the left main stem bronchus, there was marked improvement in the patient's clinical condition. Her blood pressure and pulse regained normal levels and the remainder of her postoperative course was uneventful.

Pathology Report

Pathologic examination revealed the kidney to be normal, but the tumor was a histologically malignant paraganglioma. This apparently was a nonfunctioning tumor because the patient gave no history of paroxysmal hypertensive attacks and there was no rise in blood pressure during the operative manipulation of the tumor The neoplasm was an extraadrenal tumor because during the operation the right adrenal gland was completely visualized and carefully preserved as it was separate from the tumor (Figs 422–424.)

PARAGANGLIOMA (PHEOCHROMOCYTOMA) OF THE ADRENAL GLAND (MEDULLA)

CLASSIFICATION

The adrenal medulla represents a specialized collection of nervous tissue cells, and because of the increased numbers of these cells within the gland a larger incidence of certain tumors occurs here. An orientation toward the rather bizarre neoplasms arising from these small hemiorgans is afforded by the realization that the adrenal medulla arose from the cells of the neural crest which migrated to form the sympathetic ganglia (and presumably the paraganglionic cells) The adrenal medulla is, accordingly ontogenetically related to the sympathetic ganglia. It differs from most of the extraadrenal paraganglionic cells in that those in the adrenal almost invariably manufacture epinephrine or norepinephrine and thus it manifests a pheochromo tinctorial characteristic. Many extraadrenal paraganglionic cells and tumors arising from them exhibit the same characteristics

Thus the two main groups of neoplasms arising from the adrenal medulla are

1 Those arising from the ganglionic structures (discussed *previously*)
   a. Ganglioneuroma (benign and malignant)
   b Sympathicogonioma (neuroblastoma) including sympathicoblastoma
2. Tumors of paraganglionic cells
   Pheochromocytoma It is usually benign although it has been reported malignant in 8 per cent of all cases.

It has been relatively recently that the clinical syndrome associated with tumors of the adrenal medulla, called *pheochromocytoma* by Peck in 1912, has been established. In 1922 paroxysmal hypertension due to such a neoplasm was first described, and on the basis of this symptom complex Vaquez and Conzelot made a correct preoperative diagnosis in 1926

Malignant Pheochromocytoma (Pheochromoblastoma)

Only approximately 16 such instances have been reported. They do not, as a rule present evidence of functional activity of the cells as do the benign pheochromocytomas An addisonian syndrome may supervene due to destruction

of normal adrenal tissue, or blood-borne diffuse metastases may herald the presence of the tumor Frequently the microscopic appearance is the same as a benign tumor Stout states that the presence of tumor in the blood vessel does not necessarily indicate a malignant neoplasm

Surgical resection, where possible, is the only treatment There are not enough data available to establish prognosis values

INCIDENCE MULTIPLICITY

About 90 per cent of the pheochromocytomas occur in the adrenal gland, with the right gland being involved slightly more frequently than the left According to Maier, approximately 200 adrenal tumors have been recorded in the literature, and only 19 cases of extra-adrenal tumors, three of which were located in the chest More recently an additional case of pheochromocytoma occurring intrathoracically was reported by Overholt *et al* Extraadrenal paragangliomas occur approximately once in every ten cases arising in the adrenal glands, and if we confine it to the retroperitoneal space this incidence drops slightly to about 1 in 12 cases These extraadrenal paragangliomas, like those occurring in the adrenal medulla, may or may not be physiologically active When active the disturbances resulting are identified with the pheochromocytoma In approximately 10 per cent of the cases the tumors are multiple, and of the 210 cases reviewed by Brines and Jennings there were 18 in which both adrenal glands were involved Multiple tumors in the retroperitoneal region only, or in the retroperitoneal region and the adrenal gland, have been reported Calkins and Howard record 15 patients with bilateral tumors, one-third of which were malignant There is some suggestion of a familial relationship in certain instances (Colston)

PATHOLOGY OF PHEOCHROMOCYTOMA

In over 90 per cent of the reported cases the tumor was histologically benign McGavack *et al* stated that only eight cases of malignant paraganglioma had been reported up to 1942 All were in the adrenal gland and all were said to be physiologically inactive The authors emphasize the fact that it is not possible to differentiate benign from malignant tumors by histology alone. Evidence of local invasion or metastases is required to establish a paraganglioma as being malignant Cross and Pace reported an additional case of malignant pheochromocytoma with metastasis to the cervical spine This case was unique in that the tumor was hormonally active and was associated with paroxysms of hypertension

Gross Pathologic Appearance

The tumors may vary in size from 1–15 cm in diameter They are typically well encapsulated and the outer surface is generally spherical or oval and smooth but at times may be lobulated The color varies from a greyish-pink to a reddish-brown, while the consistency varies from areas that are rather firm to others that feel softer and more cystic The cut surface has a moist, slightly bulging appearance Areas of hemorrhage are found interspersed between areas of yellow necrotic tissue and between cystic areas The cysts vary in size and may contain blood clots or a brownish fluid

Microscopic Characteristics

The cells are generally polygonal in shape and arranged in small clusters separated by a delicate vascular connective-tissue stroma The cytoplasm is acidophilic and in the hormonally active tumors there are granules in the cytoplasm which are stained brown by

chrome salts These so-called chromaffin granules when present are not necessarily found in all cells their disposition is extremely variable. The nucleus is generally large and vesicular with a nucleolus which is often prominent. Although the cells may present a bizarre appearance, mitoses are rare. The amount of necrosis and hemorrhage is variable. Stout comments on the fact that the presence of tumor cells in the blood vessels is not a criterion of malignancy since this is a frequent microscopic finding, and yet most of the tumors are benign and do not metastasize.

CLINICAL FEATURES OF PHEOCHROMOCYTOMA

The neoplasm occurs equally in both sexes and is usually found in young or middle aged adults The classical picture *is the occurrence of episodes of* paroxysmal hypertension generally associated with headaches palpitation, and precordial pain which always follows rather than precedes the rise in blood pressure Other symptoms include blanching of the face and extremities, dizziness nausea, vomiting, and a rise in body temperature. In about 25 per cent of the patients there is a persistent rather than an intermittent hypertension. An elevated BMR often as high as plus 50 or plus 60 is not an unusual finding with this tumor Many cases reported in the literature were treated initially for hyperthyroidism and showed little or no response to the usual antithyroid agents McCullough and Engel have emphasized this association of pheochromocytoma with hypertension, and believe that hypertension should make one suspicious of pheochromocytoma The association of mild diabetes with pheochromocytoma, which has also received due consideration in the literature was first emphasized by Duncan *et al* and later by Goldner The hyperglycemia generally occurs with the paroxysms of hypertension, and patients with persistent hypertension may present a persistent hyperglycemia. Richards and Hatch emphasize the fact that a patient with hypermetabolism, mild diabetes, and hypertension should be strongly suspected of having a pheochromocytoma

There is a second group of patients who go through life with no clinical signs or symptoms and yet at autopsy have a pheochromocytoma. Palmer and Castleman claim that patients in this group may die suddenly as the result of trauma or surgery

PHARMOCOLOGY OF PHEOCHROMOCYTOMA

Beer *et al.* first demonstrated the presence of a pressor substance (epinephrine) in the blood preoperatively during *a hypertensive episode in a patient* with pheochromocytoma. Others have since confirmed this and have proved the presence of increased amounts of epinephrine in the circulation in patients with pheochromocytoma. The normal adrenal medulla contains 0 4 mg of epinephrine per gram of tissue More recently Holton demonstrated the presence of increased amounts of epinephrine in patients with pheochromocytoma. Von Euler found that pheochromocytoma is capable of secreting up to 2 mg norepinephrine into the circulation and the finding of increased urinary excretion of norepinephrine is almost pathognomonic of *pheochromocytoma.* In a report of six cases by von Euler it was found that in three the tumors contained almost a pure content of norepinephrine, and all of these were located well away from the adrenal gland. In the remaining three cases there was a higher epinephrine content, these all arose from or near the adrenal gland. The normal percentage of norepinephrine in the adrenal gland according to Goldenberg is 14 to 15 per cent In pheochromocytomas

there is a very significant increase in the amount of this drug and reaches from 50 to 90 per cent

Goldenberg *et al.* have shown that epinephrine acts by increasing the cardiac output and decreasing the peripheral resistance because of vasodilation in the muscles It results in tachycardia and causes little change in the diastolic pressure It exerts its pressor action because the first effect is greater than the second. Norepinephrine, however, has little or no effect on the cardiac output but does increase peripheral resistance very considerably It results in elevation of the diastolic pressure and generally in tachycardia Because of this marked pressor effect of norepinephrine on the peripheral vessels it is generally agreed that in pheochromocytoma the hypertension is due primarily to this substance Cahill and Monteith have reported on the successful use of norepinephrine operatively and postoperatively in patients with pheochromocytoma to control the marked hypertension so often observed during these periods Goldenberg states that the rather wide range of symptoms observed in patients with pheochromocytoma is due to the varying amounts of epinephrine and norepinephrine, respectively, secreted by the tumor On analysis the norepinephrine content of these tumors has ranged from 0 95 to 6.96 mg per gram, while the content of epinephrine ranged from 0 03 to 6 5 mg per gram

DIAGNOSIS OF PHEOCHROMOCYTOMA*

Pincoffs and Shipley each first successfully diagnosed and removed a pheochromocytoma in 1929 Numerous pharmacologic diagnostic tests have been devised in recent years in an effort to establish a positive diagnosis and to exclude other conditions simulating this disease Although many of the tests will give a positive reaction with pheochromocytoma, none of them is truly specific, and therefore a negative response does not necessarily rule out the presence of a tumor The pharmacologic drugs used in the diagnostic tests for pheochromocytoma fall into two groups. (1) Those drugs which cause a discharge of pressor substance from the pheochromocytoma into the general circulation This group includes the following substances histamine, tetraethylammonium bromide, and mecholyl chloride (2) The second group of compounds is referred to as adrenergic-blocking agents. These substances presumably act by competing with the pressor compound secreted by the tumor at nerve endings. These substances include benzodioxane, dibenamine, and Regitine

Cold Pressor Test

This is a simple and often quite effective test It consists of immersing the forearm in ice water for 1 minute. In most hypertensive patients both systolic and diastolic pressure will rise by at least 15 to 20 mm of mercury The rise in blood pressure after histamine is more excessive than that during the cold pressor test Patients in whom the hypertension is due to a pheochromocytoma will fail to give a positive response to this test

Intravenous Histamine

This test was devised by Roth and Kvale in 1945. The dose given is usually 0 025 mg. of histamine or less In patients with pheochromocytoma there occurs a marked blood-pressure rise which reaches a peak between 1 and 3 minutes Headache, profuse sweating, flushing, and other symptoms associated with a

* Abstracted from J S LaDue, P J Murison, and G T Pack The use of tetraethylammonium bromide as a diagnostic test for pheochromocytoma, Ann Int Med 29 914, 1948

paroxysmal sympathetic discharge are induced. The test is not without danger particularly in patients with an elevated blood pressure to begin with, in patients with marked arteriosclerotic changes or in patients with cardiac disease The sudden severe rise in blood pressure could result in a vascular catastrophe. It is advisable to have a sympatholytic agent such as benzodioxane on hand to reverse any severe untoward effect when carrying out this test The exact mechanism of action of the histamine test is not entirely clear but in all probability it exerts a direct stimulating effect on the adrenal medulla or on the tumor

TETRAETHYLAMMONIUM BROMIDE

This substance was first used by La Due, Murlson and Pack to produce a paroxysmal rise in blood pressure in pheochromocytoma. It gives the same type of response as histamine but has an advantage over histamine in that excessive hypertension can be counteracted by having the patient sit up or stand. LaDue *et al* recommend the use of a tilting bed or table when administering tetraethylammonium bromide as a safety measure.

MECHOLYL

This was first used by Guarneri and Evans in 1948 In doses of 25 mg subcutaneously it is said to produce a paroxysmal hypertension similar to the one produced by histamine and tetraethylammonium bromide. Some patients are very sensitive to this drug and it is well to have atropine on hand whenever the drug is used.

BENZODIOXANE (933F OR PIPERIDYLMETHYL BENZODIOXANE)

This is an adrenolytic agent and acts by inhibiting certain responses of effector cells to epinephrine, norepinephrine, related amines, and sympathetic nerve impulses Goldenberg *et al.* have shown that 10 mg of benzodioxane per square meter of body surface given intravenously will produce a sharp and significant drop in the blood pressure in patients with pheochromocytoma. It is said to produce either no change or a slight elevation of arterial pressure in patients with normal pressure or with essential hypertension. Apgar recently reported that of 62 patients with proved pheochromocytoma, 59 gave a positive reaction to this test. There were only three false negative reactions She states that this drop is specific for both epinephrine and norepinephrine-secreting tumors

Others have not had quite as much success with this test. Roth states that this may be partly due to the fact that in certain of the tumors the percentage content of norepinephrine may be very high, in which case the drug will have little or no effect on the blood pressure. Wilkins *et al.* reported reactions to this compound in 8 per cent of hypertensive patients Drill noted excessive rise in blood pressure with benzodioxane in essential hypertension. It is nevertheless considered to be one of the most useful diagnostic agents we have A suitable hypertensive agent should be on hand whenever this drug is used to overcome any unexpected severe hypotensive reaction.

DIBENAMINE
(N,N DIBENZYL B-CHLOROETHYLAMINE)

This is another of the adrenolytic agents Its use as a diagnostic and therapeutic agent was first reported by Spear and Griswold. The recommended dose is 5–7 mg per kilogram body weight intravenously This drug has a more prolonged action than benzodioxane, lasting from 24 to 72 hours Its use during operative procedure in order to

counteract hypertensive episodes has been reported on by Bartels and Cattell, and by Cahill and Monteith Because of its prolonged action its use, either diagnostically or therapeutically, is considered dangerous

Regitine or C7337 (2N-p-tolyl-Nm-hydroxyphenol-aminomethyl-imidazoline Hydrochloride)

This is one of the newer drugs and, like the previous two, is also an adrenolytic agent It has been used extensively by Grimson and coworkers The recommended dose is 0 33 to 0 5 mg /kg intravenously for diagnostic purposes Iseri *et al* have recently reported on the oral use of this drug. They treated a patient successfully for 29 days prior to surgery for a functioning pheochromocytoma, using an oral dose of 25 mg. Regitine every three hours. This drug can also be used intramuscularly in doses of 2 to 2 5 mg /kg Its use during operation for pheochromocytoma, to prevent or treat excessive rise in blood pressure, has been reported by Grimson *et al* The effects of Regitine are said to parallel those of benzodioxane, indeed, it is claimed by some to be more specific in its action

Measurement of Blood or Urine Concentration of Epinephrine, Norepinephrine, and Catechol

The most direct and accurate method of diagnosing pheochromocytoma would be to measure the blood or urine concentration of epinephrine and norepinephrine before and during paroxysms of hypertension Some progress has been made in this direction by Beer and Prinzmetal, Shingleton and Baker, and by Engle and von Euler Measurement of urine or blood levels of catechol amines is proving the most reliable method for diagnosing pheochromocytoma

Radiographic Methods

These include perirenal air injection, intravenous and retrograde pyelograms, and the use of laminagrams Cahill has been a great proponent of the use of perirenal air insufflation for the diagnosis of retroperitoneal tumors. Presacral air injection frequently outlines the neoplasm very nicely The use of flat films of the abdomen and pyelograms will in most cases disclose an abnormal shadow or some displacement or deformity of the kidney. The use of laminagrams was reported by Calkins *et al.* in three patients and proved to be very valuable in correctly localizing the tumors.

TREATMENT OF PHEOCHROMOCYTOMA

The only known treatment of these tumors is complete surgical excision. A detailed discussion of various operative approaches to the retroperitoneal space is given in Chapter 28 In most cases a preoperative localization of the tumor is possible and one can, therefore, plan one's approach based on this fact. Generally speaking, the usual kidney incision combined with a resection of the twelfth rib is adequate in most instances In cases where one is unable to locate the exact site of the lesion it is perhaps best to use a transperitoneal approach, utilizing a vertical or transverse incision. In addition to exploring both adrenal regions, one must explore carefully the region of the sympathetic nerve trunks, the hilar region of the kidneys, and the lower aorta. Grimson prefers to use a transthoracic approach through the bed of the eleventh rib and through the diaphragm The left side is done first and the abdomen is explored If the tumor is not located on this side, a similar transthoracic, transdiaphragmatic retroperitoneal approach is then made through the right eleventh rib bed

The proper management of the pa-

tients before during, and after surgery is of vital importance if one is to end with a live patient. The removal of non functioning tumors is generally nothing more than a technical procedure. With the functioning paragangliomas, how ever the difficulties are many times greater and our discussion is based on the management of these. Apgar states that of the 91 reported cases of pheochromocytoma in which surgery was employed 15 were subjected to another operative procedure before the correct diagnosis was made. In the cases sus pected preoperatively of having pheochromocytoma the mortality rate was 24 per cent, whereas in the unsuspected group it was slightly higher than 50 per cent. There were, in addition, 16 other patients in whom pheochromocytoma was found only at autopsy and in whom an unrelated surgical procedure had recently been performed. Fifteen of the sixteen patients died from 2 to 48 hours postoperatively from irreversible shock. Apgar also reports on four patients with unsuspected pheochromocytoma who were operated on at the Presby terian Hospital, New York, for other lesions All died immediately postoper atively and the tumor was found again at autopsy Six additional patients in whom the tumor was found at autopsy had no symptoms suggesting pheochromocytoma The above facts merely serve to emphasize the malignant nature of this tumor physiologically speaking This is particularly so when the true nature of the lesion goes unrecognized prior to surgery One cannot stress too strongly the necessity of adequate preoperative preparation of any patient in whom there is the slightest suspicion of this tumor existing

The anesthetic management of these patients has been recently dealt with in detail by Apgar and Papper They rec ommend specifically the prevention of anoxia (due to any one of a number of causes) since it results in stimulation of the adrenal medulla, which is just what one should attempt to avoid. Induction with Sodium Pentothal followed by intratracheal nitrous oxide, oxygen, and ether is considered to be the anesthetic of choice.

During operative removal of these tu mors one must avoid excessive manipu lation and massage of the lesion and attempt to clamp the veins off as soon as possible, in order to prevent the occurrence of excessive hypertension which can result in death. The use of one of the adrenolytic agents intra venously during the operation and up to the time the tumor is removed will successfully block any excessive rise in blood pressure Episodes of hypotension and collapse have occurred in patients prior to removal of the tumor and in patients not suspected of having a pheochromocytoma and undergoing unrelated surgery This is due to excessive circulating pressor substances, resulting in acute cardiac failure and a shocklike state. As we have already seen, many deaths are directly attributable to this fact (see case report No 82)

Assuming that one has replaced vol ume for volume the blood and plasma loss during operation, one can expect postoperatively a temporary fall in blood pressure. This may be very mild and transient, and require nothing fur ther than infusions and the Trendelen burg position recommended by Bartels and Cattell. The more severe and prolonged hypotensives require more spe cific therapy Cahill and Monteith rec ommend the use of norepinephrine in doses of 4 mg. per liter of saline solution. Neosynephrine in doses of 20 mg. per liter has also been successfully used. Both these agents have a marked periph eral pressor effect with less effect on the heart than epinephrine. The infusion is usually continued for 24 hours the rate of flow being regulated to maintain a constant normotension.

Richards and Hatch maintain that

postoperative severe hypotension and death are due to a combination of acute adrenal medullary and cortical insufficiency They therefore recommend, in addition to the above measures, the use of aqueous adrenal extract, 10 cc intravenously every hour, or desoxycorticosterone acetate, 5 mg per day

CASE REPORT NO. 75 PHEOCHROMOCYTOMA WITH PAROXYSMAL HYPERTENSION, CURED BY ADRENALECTOMY

R S, a 41-year-old salesman, had been comparatively well except for insomnia, nervousness, and bilateral tinnitus of 5 years' duration, until June, 1945, when he began to have "heart attacks" These were characterized by the sudden onset of a nervousness which he described as "a pounding of my heart with the blood rushing to my head," soon followed by sweating, severe, pounding, generalized headaches, and terrific abdominal pain, "as if someone had struck me in the solar plexus with his fist" These episodes usually occurred during the day, lasted 10 to 15 minutes, and were not relieved by self-medication, hot packs, or other similar measures The patient was totally incapacitated during a seizure, being doubled up with pain, unable to suppress moans, and drenched with cold sweat When the symptoms had subsided he was left completely exhausted for an hour or more The attacks increased in frequency and severity so that the patient was loath to leave his quarters Eventually, he noticed that attacks seemed to be precipitated by his lying in bed propped on his left elbow or by a sudden twisting of his body to the left, although his symptoms occasionally appeared while he was lying on his right side He tired easily and was forced to give up tennis and other strenuous activity Almost coincidentally with the first of his attacks, he noticed a marked loss of libido

The patient consulted several physicians and was told that he had high blood pressure Sedatives were prescribed, and he was advised to avoid nervous tension and strenuous exertion His social background included an unstable childhood environment, an unhappy marriage, and recent unemployment, and this history strengthened the impression that all his complaints might be psychosomatic in origin

Examination

When the patient first presented himself at our offices on July 3, 1946, a little more than a year after his first attack, physical examination revealed a well-developed, muscular, well-nourished, white male who appeared to be in an excellent state of general health Except for blood pressure readings varying between 150 and 180 mm Hg systolic and 100 and 120 mm diastolic, the physical findings were all within normal limits Carotid-sinus pressure resulted only in a slowing of the heart rate from 90 to 85

The abdomen was soft and nontender, and no masses were palpable, although the lower pole of the right kidney was felt The extremities were symmetrical and the reflexes were normal Mild arteriovenous nicking was noted in the eye grounds

Routine hematologic studies and urine analyses revealed nothing except a trace of albuminuria The urine concentration test gave a specific gravity of 1 028, and the urea nitrogen was 27 5 mg per 100 cc of blood Phenolsulfonephthalein excretion was 15 per cent in one-half hour, 25 per cent in one hour, and 5 per cent in the second hour, a total excretion of 30 per cent (September 11, 1946) By September 16, 1946, the phenolsulfonephthalein excretion had risen to 45 per cent in one-half hour and 60 per cent in one hour, with a total two-hour excretion of 60 per cent The urea nitrogen had fallen to 18 4 mg, and the total protein was 6 10 gm, with 4 30 gm of albumin and 1 80 gm of globulin The blood cholesterol was 441 mg, and the blood sugar 134 mg per 100 cc of blood Wassermann and Kahn reactions were negative

An intravenous pyelogram showed that the right kidney was flattened at its superior pole and displaced downward by a soft-tissue mass A roentgenogram of the chest was within normal limits, the electrocardiogram showed slight left axis deviation with one millimeter elevation of S T_1 and a 1 mm depression of S T_2 and S T_3

On the patient's second office visit, he was asked to try to produce an attack. He succeeded in doing so after 5 minutes of lying on his left side and raising his shoulder by leaning on his left arm He then complained of a pounding headache palpitation, dizziness and severe epigastric pain. His skin was blanched, and he walked about the room doubled over and moaning with pain. The skin was cold and moist, particularly at the extremities. The pupils were somewhat dilated, and the retinal arterioles could be seen to contract and relax. Respirations were increased (16 to 25) and were somewhat deeper the heart was regular at 130 beats per minute, and a moderately loud, blowing, apical systolic murmur appeared with an accentuated A_2. The blood pressure rose above 300 mm Hg systolic (limit of range of the sphygmomanometer) and 160 mm diastolic, falling to 180 mm. Hg systolic and 150 mm. diastolic within 10 minutes.

A presumptive diagnosis of pheochromocytoma was made and the patient was admitted to Flower and Fifth Avenue Hospitals on September 8 1946 The reactions of the patient to the intravenous administration of histamine, tetraethylammonium bromide and saline were studied preoperatively and are considered in detail later

Treatment

On September 26 1946 an 8 × 5 cm. tumor overlying and displacing the superior pole of the right kidney was removed through an oblique right lumbar incision The pedicle was isolated by blunt dissection and was rapidly ligated, and the encapsulated tumor was removed within four minutes, thus reducing manipulation of the tumor to a minimum.

Since most authors have reported severe shock following removal of these tumors, several precautions were taken The patient was given spinal anesthesia of Nupercaine, using 5 cc. of a 1 1500 solution, since the specific gravity of this solution is lighter than that of spinal fluid. This should have resulted in a relatively greater paralysis of the splanchnic nerves on the right than on the left with the patient lying on his left side at operation. Theoretically this should produce less anesthesia of the splanchnic nerves on the left and should allow them to continue to function after removal of the adrenal tumor on the right. The blood pressure was 180 mm Hg systolic and 105 mm diastolic just before handling of the tumor was begun and it rose to 250 mm. systolic and 130 mm diastolic during the manipulation necessary to removal. With ligation of the pedicle the blood pressure promptly fell to shock levels. Intravenous plasma and two 50 mg intravenous injections of ephedrine brought the reading to 100 to 80 mm Hg systolic and 70 to 50 mm diastolic within three minutes Postoperatively the blood pressure did not fall below 95 mm Hg systolic and 55 mm diastolic, and the pulse rate varied between 100 and 125

Postoperative Course

Convalescence was rapid and uneventful, the patient was out of bed on the second postoperative day and went home on the tenth postoperative day

Daily blood pressure recordings for some time thereafter and monthly checkup measurements have not exceeded 130 mm Hg systolic and 70 mm diastolic. The patient complained for two weeks of coldness and blueness of his hands and feet, but this symptom disappeared after the administration of 0 1 gm of papaverine four times daily for 10 days The eye grounds returned to a normal appearance, and the phenolsulfonephthalein excretion was 68 per cent in one-half hour and 77 per cent in one hour with a total two-hour excretion of 77 per cent on October 29 1946 The patient has had no further attacks and his sense of well-being and libido are completely restored.

Pathology Report

"The tumor is a globular but somewhat irregular encapsulated mass, weighing 298 grams. Upon the surface, small, pale brown areas, evidently adrenal cortical tissue can be identified. Upon section, the tumor tissue appears grayish white in some areas and reddish brown in others. The latter discoloration appears to be due to degeneration and hemorrhage Two cysts are present these occupy the central half of the tumor

and they are filled with bloody fluid which coagulates upon standing

"Microscopic examination of the tumor shows a marked variation in the shape of the cells, some being round and oval while others are polygonal Some of the cells appear light in color, almost hydropic, while others are small and dark staining There are no definite anaplastic changes seen The tissue which was fixed in chrome salts has become brown in color The pathological diagnosis is benign pheochromocytoma (adrenal) "

The tumoi contained 8 gm epinephrine in 200 gm of tumor tissue (equivalent to 8 L of a 1 1000 solution of epinephrine) Ninety-eight grams were fluid with a concentration of 100 mg to 0 1 per cent The concentration of epinephrine was equal to 4 0 per cent of tissue by weight

Discussion of Case Report No 75

The patient's reactions to intravenous injections—first, 2 cc saline solution containing 0 025 mg of histamine phosphate, then a 2 cc solution containing 400 mg tetraethylammonium bromide, and finally of 2 cc. saline, are compared in Figures 425 and 426

Within 1 minute after the administration of histamine the patient developed a typical attack, associated with a rise in blood pressure from 160 mm Hg systolic and 105 mm diastolic to 280 mm. systolic and 160 mm diastolic The reading returned approximately to normal within 5 minutes The pulse rate rose from 94 to 116 and then fell to 96 Although the resting blood pressure was somewhat higher before tetraethylammonium bromide was given, the response was just as pronounced and lasted considerably longer The reading rose from a basal level of 175 mm Hg systolic and 105 mm diastolic to 270 mm systolic and 160 mm diastolic in 30 seconds, and the elevation lasted 15 minutes The pulse rate rose from 75 to 130 and returned to 90 The decrease in the blood pressure when the patient changed from a supine position to standing erect was dramatic, the reading falling from 230 mm. Hg systolic and 125 mm diastolic to 95 mm systolic and 80 mm diastolic

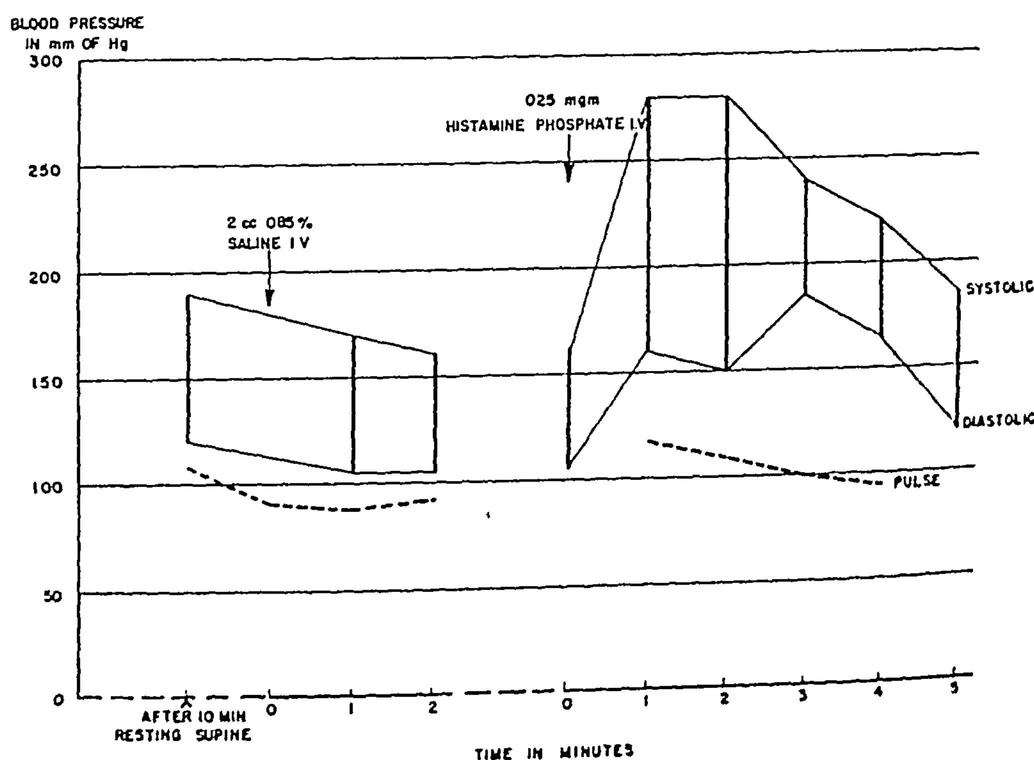


Fig 425 Pheochromocytoma (preoperative) Graph showing blood pressure and pulse response to the intravenous injection of 0 025 mg of histamine diphosphate and to the intravenous injection of 2 cc of saline (Case report No 75) (LaDue, Murison, and Pack, Ann Int Med 29 914, 1948)

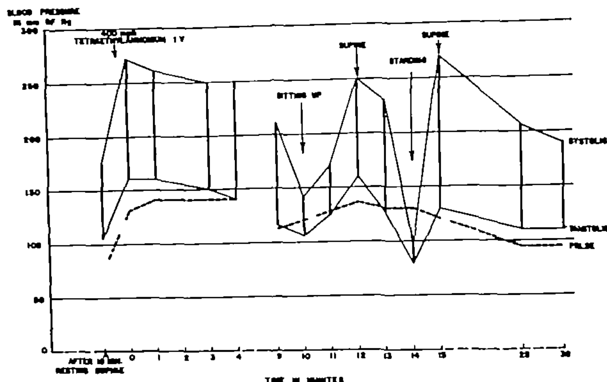


Fig. 426 Pheochromocytoma (preoperative) Graph showing blood pressure and pulse response to the intravenous injection of 400 mg. of tetraethylammonium bromide and to the injection of 2 cc. of saline. Changes in blood pressure and pulse rate resulting from shifting from sitting, standing, and supine positions are indicated. (Case report No. 75) (LaDue Murison, and Pack, Ann. Int. Med 29 914, 1948.)

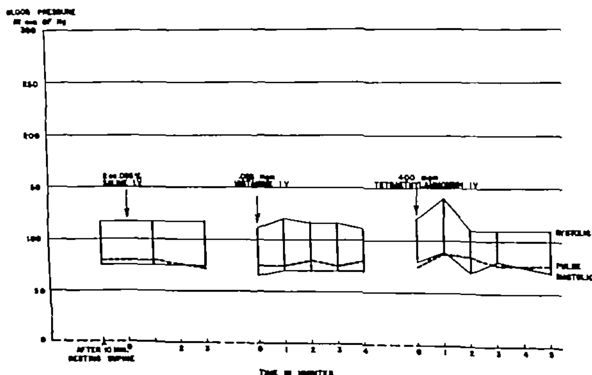


Fig. 427 Pheochromocytoma. Graph showing the postoperative absence of response to the intravenous injection of histamine tetraethylammonium, and saline. (Case report No. 75) (LaDue Murison, and Pack, Ann. Int. Med. 29 914, 1948.)

When the 2 cc injection of saline was given, no detectable change in the blood pressure or pulse rate occurred

On October 15, 1946, approximately two months postoperatively, the above tests were repeated, and the patient evinced no reaction to the injection of histamine, tetraethylammonium bromide, or saline (Fig 427)

It is reasonable to assume that the preoperative hypertension found in this patient resulted from the oversecretion of epinephrine and that the paroxysmal attacks were due to the sudden release of large amounts of epinephrine into the blood stream Heavy exertion, positional changes, and manipulation of the tumor all resulted in sudden hypertension of high degree, undoubtedly due to release of epinephrine simply by mechanical pressure on the tumor Preoperatively, the only times when normal blood pressure readings were obtained were when the patient had been lying quietly on his back for an hour or more The effect of massage or pressure in precipitating typical attacks has been emphasized It is also noteworthy that high concentrations of a pressorlike substance have been found in the blood of patients during seizures

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CHAPTER 24

Sarcomas of Undetermined Histogenesis

SARCOMAS of undetermined histogenesis form an indefinite group comprising the so-called spindle-cell, round-cell, polyhedral-cell, and alveolar sarcomas which are not included in those groups with well-determined histogenesis In any large series of sarcomas there is bound to be a group which defies classification. However competent the pathologist, aided by selective staining, tissue culture and study of gross anatomic characteristics of these neoplasms, there always remains a residue which cannot be classified as regards their histogenesis In this "catchall" category we futilely consign the sarcomas of undetermined histogenesis With such competent tumor pathologists as James Ewing, Fred W Stewart, Frank Foote, and George K. Higgins over a third of the sarcomas of this series could not be classified. One must look askance at any large reported series in which every sarcoma has been identified as to its cell origin In our series of 717 sarcomas the largest group was composed of sarcomas whose exact histogenesis could not be determined There were 261 such neoplasms 36 4 per cent of all sarcomas

There was no sexual predilection for this heterogeneous group of tumors, as 54 4 per cent occurred in males and 45 6 per cent occurred in females The average age of patients with unclassified sarcomas was 36 years. In contrast to other sarcomas there was practically a constant distribution of the same number of cases for each of the five-year age periods from birth to 17 years This caused an incidence of occurrence which gradually increased with advancing years to the quinquennium 65 to 69 years, when the maximum incidence was found. Thirty-two per cent were under 25 years of age, and this number constituted 6 6 per cent of all malignant tumors occurring in patients under 25 years of age.

Nothing definite can be stated concerning the clinical or pathologic features of this group of tumors, because by definition this group is a repository for those sarcomas which cannot be accurately classified. One might properly question the comparative curability of these different sarcomas because of the likelihood that sarcomas of undetermined histogenesis contained the most malignant tumors which might by subtraction give a false higher rate of curability for the indefinable types This assumption is incorrect, as evidenced by the five-year rates of definitive cures 40 8 per cent for sarcomas of undetermined histogenesis (Table 85) as compared with 39.2 per cent for the entire collective series of soft part sarcomas

TABLE 85 TYPE OF TREATMENT OF SARCOMA OF UNDETERMINED HISTOGENESIS IN RELATION TO FIVE-YEAR SURVIVAL WITHOUT SARCOMA, BASED ON DETERMINATE CASES

Type of Treatment	*Total Cases*			*Primary Operable*			*Recurrent Operable*			*Inoperable Cases*
		5-year Cures			*5-year Cures*			*5-year Cures*		
	Total Cases	*Number*	*Per Cent*	*Total Cases*	*Number*	*Per Cent*	*Total Cases*	*Number*	*Per Cent*	*Number*
Total cases	147	60	40.8	26	15	57.7	62	32	51.6	12
Excision only	25	18	72.0	11	9	81.8	12	9	75.0	2
Excision and irradiation	33	19	57.6	9	5	55.6	24	14	58.3	0
Amputation	19	4	21.1	4	0	0.0	14	4	28.6	1
Dissection	4	2	50.0	0	0	0.0	4	2	50.0	0
Interscapulothoracic amputation	3	2	66.7	0	0	0.0	3	2	66.7	0
Hip-joint disarticulation	6	1	16.7	1	0	0.0	5	1	20.0	0
Postoperative prophylactic irradiation	17	13	76.5	0	0	0.0	0	0	0.0	0
Irradiation only	38	1	2.6	1	1	100.0	0	0	0.0	37
No treatment given	2	0	0.0	0	0	0.0	0	0	0.0	2

ALVEOLAR SOFT-PART SARCOMA

Christopherson, Foote, and Stewart have presented data depicting the structural and clinical features of one group of these sarcomas of uncertain histogenesis, "the alveolar soft-part sarcomas." During a 17-year period they were able to collect 12 cases of the alveolar soft-part sarcomas. Of the 12 patients, 10 were females, and the ages ranged from 3 to 38 years, with most in their late teens or early twenties and only one over 30 years old. The usual history was that of a slowly growing, asymptomatic mass in one of the extremities. Most of the tumors were usually well circumscribed and at least partially encapsulated. Occasionally there was gross invasion at one or more sites. As a rule the dissection from the contiguous tissues could be accomplished with ease. A local excision was performed in all their patients except for the performance of a low thigh amputation in one whose tibia and fibula were invaded by tumor. Recurrences of tumor occurred in three patients, of whom all later developed metastases and two have died. Radiation therapy was used in addition to surgery in three patients, and of these two have succumbed from metastases. Five of the 12 patients are known to have developed metastases, and in each of these metastases to the lung occurred; in addition the brain was involved in two cases. Four of this group of 12 patients have survived without recurrence or metastasis for from 5 to 15 years after removal of the primary tumor. In one patient an 18-year span elapsed between the excision of the primary tumor and the clinical recognition of pulmonary metastases, for which a lobectomy was performed. The patient was also found to have hepatic metastases at the time of the lobectomy. She succumbed 17 months after the lobectomy with generalized metastases (case report No. 76).

Christopherson, Foote, and Stewart describe the histopathology of these tumors as follows:



FIG. 428 Sarcoma of undetermined histogenesis (alveolar-cell type) The rather uniform alveoli are composed of large, polyhedral-to-oval cells with pale, finely granular cytoplasm and eccentric vesicular nuclei. The delicate septa are well shown but the endothelium-lined blood spaces are not as conspicuous as usual. (*Courtesy* Dr Fred W Stewart.)



FIG. 429 *Sarcoma of undetermined histogenesis* (alveolar-cell type) Photograph taken 6 years after local excision and x ray therapy This patient developed metastases 18 years after the initial treatment (Case report No. 76.)

Perhaps the most striking feature of the alveolar soft part sarcoma is the basic uniformity throughout a given tumor and the similarity of one tumor to another This uniform pattern is preserved in the metastatic lesions that are available for study The tumor is characterized by the pseudoalveolar or organoid, arrangement of the cells in relation to numerous delicate endothelial lined vascular channels and septa. The pattern is somewhat reminiscent of that found in paraganglionomas and other endocrine tumors In sections impregnated with silver the septa are seen to separate the individual alveolar group from the vascular channel, or from similar adjacent groups of cells. There are no reticulin fibers between the individual cells, which either form compact groups of from four to five or perhaps fifty cells, as seen in any one plane of section, or present a more strictly alveolar form, with a peripheral row of cells and a central space devoid of organized structure The latter arrangement was often seen especially in some of the earlier cases examined, and it was this pattern that was responsible for the term "alveolar soft part sarcoma" It is possible that this may represent an artifact produced by the dropping out of the central cells. However its occurrence is consistent enough to make it a definite feature of the tumor and, if extensive enough may lead to an erroneous diagnosis of adenocarcinoma

In some instances small groups of cells are seen budding into vascular channels in a glomerular fashion pushing the endothelial lining before them In no instance did we find evidence of a transition between endothelial and tumor cells This method of growth has some significance, we believe in that tumor masses were often found within the lumina of vessels in or near the capsule. Vascular invasion was seen in the more favorably behaving tumors as well as in those that metastasized and so was of no apparent value in the prognosis of an individual case.

The component cell is large, oval to polyhedral, usually with distinct cell boundaries. The abundant cytoplasm take a light eosinophilic hue in hematoxylin-and-eosin preparations It stains light brown with both Masson trichrome and *phosphotungstic* acid hematoxylin The cytoplasm is

finely granular or reticulated with occasional vacuoles that usually do not stain with mucicarmine, osmic acid, or Sudan stains, although in degenerated areas some of the vacuoles are sudanophilic In a single instance in which stains for glycogen were done, small amounts were demonstrated in a finely granular distribution throughout many of the cells The cytoplasm is never as deeply acidophilic as that in classical rhabdomyosarcoma nor is there any suggestion of striations, or elongated, ribbon-like cells suggestive of known types of muscle tumors The coarse granularity characteristic of myoblastoma is not present, although the similarity of individual cells to those found in myoblastomas is admittedly great An eccentrically placed vesicular nucleus containing one or more distinct nucleoli is usually present As a rule, there is minimal variation in the nuclei, although an occasional cell is binucleated and larger than usual, and a few nuclei are hyperchromatic Mitoses are usually present but never in great numbers Variations in cytology appear to be more related to degeneration than to activity [One case] is the notable exception to this In these sections, several large anaplastic-appearing cells were encountered, although the basic histology and morphology are preserved elsewhere in the tumor In no other instance did we consider the histological variation of sufficient degree to venture a prediction as to the malignant potentiality of the individual case This reluctance to prognosticate on histological grounds alone was further fortified by the well-organized, unaltered appearance of metastatic lesions in some of the other cases

Further observations will undoubtedly lead to the recognition of the cell of origin of alveolar soft-part sarcomas which will permit the removal of this subdivision from the list of sarcomas of undetermined histogenesis

With improved technics for histologic identification and increased experience with all sarcomas, it is anticipated that this group of unclassified sarcomas may gradually dwindle in number as they are catalogued into their respective subdivisions, and some day this classification, necessitated by ignorance, will become extinct

CASE REPORT NO. 76
ALVEOLAR SOFT-PART SARCOMA WITH GENERALIZED METASTASES

D L, a 19-year-old girl, was first seen by one of us (G T P.) on July 3, 1934 Two years prior to this she had fallen in the gymnasium, striking the right buttock There was no serious reaction to the fall until February, 1933, when she fell while sleigh riding and struck the same area. She discovered a lump the size of a golf ball She did nothing about this until March, 1934 By this time the lump had increased to the size of a small grapefruit and had begun to ache Her local physician advised an operation, but she would not consent to operation although she continued to have pain Two weeks before admission here a local excision was performed elsewhere Following the operation the patient noticed swelling in the inguinal region which was tender on palpation (Fig 429)

Diagnosis

A review of the submitted slide revealed "Highly malignant alveolar liposarcoma, radiosensitive and capable of rapidly generalizing metastases" Later, on September 30, 1946, it was felt that this was not a liposarcoma but should be in the group of sarcomas whose histogenesis cannot be determined

Treatment

The treatment given was high-voltage x-ray therapy to the buttock region This was carried out on July 3 and on August 27, 1934, with the following factors 750 r × 2, 200 kv, filter ½ Cu, 50 cm target-skin distance with a port 21 × 18 cm

Course

She remained well until 1951, when roentgenograms revealed metastases to the

lung A lobectomy was performed September 21 1951 Histologic examination of the excised pulmonary tumor revealed it to be a metastatic alveolar-cell sarcoma. She succumbed 17 months later An autopsy revealed metastases to the liver spleen, pancreas heart, kidneys, lung, and adrenal glands.

CASE REPORT NO 77: FUNGATING SARCOMA OF THE ARM IN A TWO YEAR OLD CHILD; AMPUTATION; TWENTY EIGHT YEAR CURE

In January 1928 when this patient J R. was 18 months of age, her mother noticed a nodule in the skin of the right forearm, it



FIG. 430 Sarcoma of undetermined histogenesis. (*Left*) Fungation of recurrent sarcoma of arm through wound of *previous incomplete* excision in a 2 year-old child. (*Right*) Appearance after amputation. Patient living and well 28 years later Now married and mother of one child. (Case report No 77)

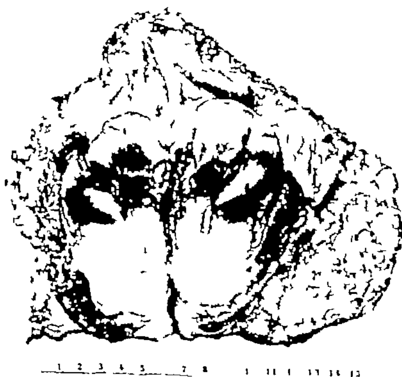


FIG. 431 Dissected gross specimen of tumor of undetermined histogenesis (Fig. 430) *illustrating* myxomatous degeneration. (Case report No. 77)

rew rapidly during the next 5 weeks he skin remained intact over the lump On ebruary 23, 1928, this lump was excised sewhere and a diagnosis made of malig-ant tumor The patient then received two dium treatments without appreciable enefit. Ten days before registration at our linic, the skin overlying the tumor sloughed way leaving a fungating, bleeding mass

She was first seen on July 30, 1928, at hich time there was a huge, ulcerating, re-urrent tumor involving the soft tissues of e right forearm The tumor measured 12 m in width and 16 cm in length It ex-nded from just above the wrist to two iches above the elbow The tumor was ingating through the skin (Fig 430) A oentgenogram of the chest revealed no evi-ence of pulmonary metastasis On August , 1928, the right arm was amputated at a istance of three inches from the shoulder joint A blood transfusion was given at the same time On microscopic examination the tumor was reported as a myxosarcoma of undetermined histogenesis (Fig 431) The gross character of the tumor was such that one could not identify the tissues of origin

Course

The patient has remained in good health to date She is married, has delivered a normal child, and is apparently cured 28 years after the amputation for sarcoma of the arm

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SECTION IV

Sarcomas of the Soft Somatic Tissues in Infants and Children

CHAPTER 25

Sarcomas of the Soft Somatic Tissues in Infants and Children

MALIGNANT tumors destroy the lives of more infants and children than do most other diseases including tuberculosis, heart disease poliomyelitis, etc. Studies have been conducted pertaining to the etiology and treatment of practically all pathologic processes in the young human with the exception of cancer Oncology in children has been neglected because of a number of misconceptions pertaining to childhood cancer

Among these misconceptions are (1) It is so rare that it does not warrant extensive investigation (Although relatively infrequent it nevertheless constitutes the major threat to the life of the developing infant and child.) (2) It is universally fatal, therefore a pessimistic attitude prevails (It shall be shown that this concept is entirely erroneous) (3) Cancer in infants and children has such a proclivity to growth and propensity to metastasize that it resists every effort at local control. (Although certain tumors of childhood do tend to grow more rapidly than do their counterparts in the adult, proper therapy can control most childhood neoplasms. Contrariwise certain neoplasms in children may present a highly malignant histologic appearance but behave benignly from a clinical standpoint, e g melanomas, certain liposarcomas) (4) Cancer in childhood represents an end stage of a prenatal abnormality and at the time the cancer is noted clinically it is already widespread (This concept is fallacious and most childhood neoplasms are localized when first discovered.) These misconceptions and others not listed reveal a trend of thought which currently prevails concerning cancer in infants and children

An understanding of the natural history of malignant tumors in childhood and their points of similarity and divergence from cancer in the adult would permit the development of therapeutic methods and offer scales for measuring prognosis A critical evaluation of the efficiency of the therapeutic modalities utilized could then be made.

This chapter presents the results of an analysis of the clinical courses correlated with the histologic details of soft somatic tissue sarcomas of infancy and childhood Methods of treatment are evaluated and end results presented.

INCIDENCE OF CANCER IN CHILDREN

Cancer, one of the greatest threats to the lives of the infant and child, is increasing in frequency It is the third greatest cause of death in children from 1 to 14 years of age (Table 86), being exceeded by accidental deaths and pneumonia, and the second foremost cause of death in youths between 5 and 14 years, being exceeded only by accidents This high death rate is a rather recent development For example, 20 years ago cancer was not even listed in the group of the ten most frequent causes of death in children It is believed that there has not been an absolute increase in the incidence of cancer in children, but, rather, that the precipitous decline of the death rate from neonatal and infectious diseases focuses attention upon the frequency with which cancer kills babies and children Over 2000 infants and children between the ages of 1 and 14 years died in the

TABLE 86 LEADING CAUSES OF DEATH FOR CHILDREN AGED ONE THROUGH FOURTEEN YEARS IN THE UNITED STATES IN 1947

Cause of Death	*Number*	*Per Cent of Total*
Accidental deaths	10,731	32 2
Pneumonia	3,240	9 7
Cancer, including leukemia	2,490	7 5
Tuberculosis	1,328	4 0
Heart disease	1,131	3 4
Congenital malformation of cardiovascular system	920	2 8
Meningitis	823	2 5
Congenital malformation of nervous system	810	2 4
Diarrhea, enteritis	724	2 2
Appendicitis	700	2 1
Nephritis	668	2 0
Diphtheria	637	1 9
All others	9,142	27 3
TOTAL	33,344	100 0

TABLE 87 CAUSES OF DEATH IN NEW YORK CITY, 1950

	Age				
	0–4	*5–9*	*10–14*	*11–19*	*All Ages*
1. Total (all causes)	4,452	273	196	373	79,082
2 Infections and parasitic disease	119	35	22	53	2,873
3. Tuberculosis (all forms)	61	10	7	36	2,321
4 Neoplasms	130	71	41	53	15,831
5 Allergic, endocrine system, metabolic, nutritional	11	5	3	2	1,919
6 Blood and blood-forming organs	10	4	1	5	163
7 Nervous system and sense organs	63	18	13	13	5,686
8 Circulatory system	4	9	31	47	36,659
9 Respiratory system	525	28	14	15	2,917
Pneumonia (all forms)	40	14	10	9	239
10 Digestive system	129	15	3	6	3,293
11. Genitourinary system	15	10	9	26	1,135
12. Bones and organs of movement	8	0	1	0	102
13. Certain diseases of early infancy	2,521	0	0	0	2,521
Birth injury	369	0	0	0	369
14 Accidents, poisoning, and violence	196	66	47	101	1,521
15 Homicides	34	0	1	19	329

Based on figures of New York City Department of Health Statistical Division

United States from cancer in 1947 In 1948 cancer including leukemia, caused 7.3 per cent of all deaths of children between 1 and 14 years of age.

The causes of death in New York City for the year 1950 are presented in Table 87 The high incidence of deaths from neoplastic disease in children is evident.

TYPES OF CANCER IN INFANTS AND CHILDREN

Unlike cancer in adults, carcinoma is *very rare in children*. Sarcomas, embryomas, and mixed tumors are most frequent. Of 219 malignant tumors at Children's Memorial Hospital, Chicago and the University of Chicago only 1 carcinoma (of the liver with juvenile cirrhosis) was encountered. At the Babies Hospital in New York, of 175 malignant tumors, 111 were of mesodermal origin, 5 were teratomas 10 were carcinomas, and 49 were of the nervous system. Although different institutions with selective criteria for admission may show certain variables of incidence and types of childhood cancer it is established that sarcomas are by far the most frequent form of cancer in children. In Table 88 are correlated the chronologic and physiologic ages of man and the most frequent neoplasms are listed for the different age spans

LOCATION OF TUMORS IN INFANTS AND CHILDREN

BENIGN TUMORS

In a series of 600 surgical specimens from infants and children, Steiner noted that 22 per cent were malignant tumors, 63 per cent were benign tumors and 15 per cent were nonneoplastic.

The most frequent benign tumors were polyps, papillomas and polypoid adenomas of such epithelial structures as the larynx, rectum, nose ear etc., and in decreasing frequency hemangiomas, dermoids, epidermoids, fibromas, lymphangiomas, etc. Tumors of the connective-tissue group (fibromas, lipomas, neurofibromas lipofibromas, chondromas and osteochondromas) rated third in order of frequency

A finding of interest from the necropsy series was that benign tumors noted as an incidental finding during necropsies in adults are not seen in children These include uterine polyps, and fibroids adenomas of the thyroid, adrenal cortex, and kidney adenomatous hyperplasia of the prostate· polyps and polypoid adenomas of the colon, hemangiomas of the liver· fibroadenomas of the mammary glands and papillomas of the urinary bladder

CANCER

The tissues most frequently involved by cancer in children (from 1718 cases of children's cancer reported by Andersen) are in order of decreasing frequency

	Number of children
Central nervous system	380
Bones	365
Eye and orbit	235
Genitourinary system	230
Lymphatic system	204
Soft somatic tissue sarcoma	144
Pharynx	36
Skin	31
Abdomen	19
Gastrointestinal tract	21
Gynecologic	25
Liver	13
Miscellaneous	18
Salivary glands	7
Lung	5
Pancreas	3
Lip	2

TABLE 88 MALIGNANT TUMORS CORRELATED TO AGE PERIODS

	Infancy	*Childhood*	*Presex*	*Puberty*	*Maturity*	*Senescence*
Chronologic development	1–10 mo	10 mo to 7th or 8th yr	8th to 14th yr	To 28th yr (males) To 24th yr (females)		
Physiologic development	Birth to independent nutrition	To development of senses	Intermediate stage between childhood and adulthood	From puberty to end of growth period	From end of growth to sexual decline (males) and to menopause (females)	From menopause (females) and from sexual decline (males) to death
Most frequent tumors	Wilms's adenomyosarcoma of the kidney Ocular glioma	Ocular glioma Wilms's tumor	Usually free of malignant tumors	Endothelial myeloma Thymoma Gliosarcoma Testicular sarcoma	Great host of malignant tumors	Basal-cell epithelioma of skin Squamous-cell carcinoma of skin, lip, buccal mucosa, floor of mouth, and vulva Carcinoma of prostate gland

SARCOMAS IN CHILDREN

INCIDENCE

Sarcomas of the soft somatic tissues of children vary in incidence with the different reports from various hospitals At the Mayo Clinic, of 750 malignant tumors in infants and children, there were only 18 instances of sarcomas of the soft somatic tissues Duzan in 1876 reported on 183 tumors of infancy and childhood, and Picot in 1883 reviewed 424 tumors of childhood. Neither of these early authors mentioned sarcomas of the soft somatic tissue.

Arey reporting from St. Christopher s Hospital for Children and Temple University School of Medicine, Philadelphia, presented 62 malignant tumors in children observed during an 18-month period. The most frequent form was sarcoma of the soft tissues, which comprised 18 per cent of all the childhood cancers.

Vidaback, reporting from Denmark, indicates that of 276 childhood cancers recorded from 1942 to 1944 the most frequent were the lymphomas (30 per cent) while the second most frequent form was sarcoma of the soft somatic tissues (20 per cent)

At the University of Michigan, 272 malignant tumors of children were recorded between 1943 and 1947 with only 12 instances of soft tissue sarcoma.

From the Boston City Hospital, Ritvo *et al* reported 72 instances of childhood cancer during a 25-year period, of which sarcomas of the soft tissues comprised 9 per cent Scotti reported 8 sarcomas of the soft tissues in a total of 64 children observed at the New York Post Graduate Hospital. Blacklock, reviewing 100 childhood cancers found sarcomas most frequent (33 per cent) At the Birmingham Children s Hospital, England, no sarcomas of the soft tissues were reported by Smellie. Lawrence and Donlan, reporting from Indiana University listed 42 malignant tumors of the soft somatic tissues in a total of 370 malignant neoplasms in children under 15 years of age.

These data indicate that sarcomas of the soft tissues are a major form of cancer in childhood. The different incidences of this form of cancer reported from the different hospitals are undoubtedly the result of selective admissions in certain institutions

PATHOGENESIS

Sarcomas of the soft somatic tissues of infants and children represent a histologic and clinical entity which, although not common constitutes, nevertheless one of the major forms of cancer of the developing infant and child. The presence of a malignant neoplasm in a newborn infant offers material for great speculation concerning etiology and pathogenesis The cancerogen must be potent, for it has a short period to exert its influence (maximum of nine months) Willis has indicated that the genesis of teratomas of infants must be related to the chemistry of the "organizers" or growth hormones which determine the orderly developmental patterns and that the locations of teratomas suggest growth disturbances from the primary axis—the notochord and contiguous structures—which is derived by invagination at Hensen s node in the early embryo and constitutes the primary organizer He indicates that blastulas deprived of their primary organizer regions can grow and differentiate into a variety of tissues but that they do so in a chaotic manner and without forming an axis or defined organs He suggests that teratomas may represent clusters of tissue which early escaped the action of the primary organizer

Localized chemical aberrations within

the embryo could be responsible for the formation of sarcomas of the soft somatic tissues. Sometimes maternal influences will produce localized effects, for example, rubella in the human mother frequently produces cataracts in the offspring. It has been shown in animals that insulin given to the parent results in congenital deformities, possibly by altering intrauterine environment (Lawrence).

Certain postnatal reactions of fibrous tissue give suggestions of prenatal influences which may be factors in sarcomatous formations. The reaction of fibroblasts to testicular extract represents a recapitulation of their normal developmental history with acceleration of maturation, and suggests that in normal development, aging, and repair there is a progressive series of changes, with a shift from the amorphous to the fibrous elements of the intercellular substance. The nature of the alterations is dependent upon many factors including species, race, familial factors, and even individual variations. For example, if 20-methylcholanthrene is injected into guinea pigs, 20 per cent of the animals develop liposarcoma, but if the same chemical is injected into mice, none develops liposarcoma (species alteration).

The reason for the differences in the behavior of cancer in the very young from that in older individuals is not understood. Certain cancers can well be explained on the basis of Cohnheim's theory of misplaced cell rests. Another important factor is the difference between the anatomic and physiologic ages of different structures within the organism during a given age of the individual. Thus, at the time of birth certain organs may be considered aged and commence toward their involutional state, *e g*, the thymus. Other structures, such as the vaginal epithelium, may be mature as a result of the influence of maternal hormones, and others, *e g*, the breast, may lie dormant awaiting their selective stimuli to maturate. Due to certain inborn errors of metabolism a speeding-up of the aging process occurs either for certain structures, such as the epidermis in xeroderma pigmentosa, or for the entire organism, as seen in the Ehlers-Danlos syndrome. An example of senility at birth is seen in the placenta. Its calcareous, fibrotic, atrophic, and vascular changes are characteristic of old age. The placenta has the shortest life of any human organ, yet at times it is subject to the development of cancer (chorioepithelioma). This cancer formation is in keeping with its anatomic age.

The more frequent occurrence of sarcoma in infants and children than in adults is not completely understood. Chronic irritation has been demonstrated to produce certain sarcomas, as sarcoma in a burn scar. Whether irritating factors excite neoplastic formation during prenatal life is not known. As the individual becomes older, and as a result of the normal metabolic wear and tear on an organism, compounded by stimuli for fibrous propagation from infection, trauma, or other noxious agents, it would seem that a richer soil for sarcomatous formation exists in the adult than in the child, but this situation does not prevail, as sarcomas occur more frequently in children than do neoplasms of epithelial structures.

It is beyond the scope of this discussion to pursue this fascinating line of thought further, but the evidence is presented to indicate that prenatal influences can affect a localized segment of tissue, with resultant formation of an entirely localized sarcoma. Contrary to certain opinions, it does not reflect a generalized abnormality of the supporting structures of the organism and is thus akin to most sarcomas in the adult.

The stimulus for certain neoplasms is transmitted from parent to offspring via the genes and adheres to genetic laws, *e g*, retinoblastoma, hereditary

cartilaginous exostosis, familial polyposis of the colon, and multiple neurofibromatosis and lipomatosis In most sarcomas of the soft somatic tissues however either a limited portion of tissue has undergone sarcomatous transformation, as in rhabdomyosarcoma or a larger segment of tissue may be doomed to sarcomatous formation which occurs at variable postnatal periods e g neurilemmoma invading an entire major nerve trunk from its point of emergence from the spinal tract to its fibrillar ramifications.

Such ontogenetic background aids in formulating principles for treating sarcomas of the soft somatic tissues in the infant and child. It forces the physician to seek out the presence of certain neoplasms if a parent had suffered its presence (*e.g.*, retinoblastoma) it offers the surgeon criteria for extirpating organs which are the seat of certain premalignant tumefactions (familial colonic polyps) and it routes the surgeon on his course for boldly treating localized sarcomas of the soft tissues in infants and children. The knowledge that they represent localized and at times limited tissue aberrations and not generalized structural dysfunction permits the surgeon to strive for complete eradication of the neoplasm and its bed.

CLASSIFICATION OF SARCOMAS OF SOFT SOMATIC TISSUES IN CHILDREN

The supporting organs of the body are the frequent seat of both benign and malignant tumors in children Of the six tissues in juveniles most frequently afflicted by cancer (central nervous system, bone, eyes, genitourinary system blood and lymphoid system, and soft somatic tissues) neoplasms of the central nervous system, eye, and kidney and lymphomas have been the subjects of many reports in the literature Sarcomas of the soft somatic tissue however have received only scant attention and most publications consist only of individual case reports

This chapter reviews 51 sarcomas of the soft somatic tissues in children, some treated at the Mixed Tumor Service of the Memorial Cancer Center and others at the Pack Medical Group The group comprised 7 1 per cent of all patients (717) observed bearing soft somatic tissue sarcomas

The most frequent classified sarcoma noted in this series was the malignant neurilemmoma, and its incidence in children under 15 years of age comprised 15.2 per cent of all malignant neurilemmomas Although as many liposarcomas were observed as were malignant neurilemmomas, the number seen in children was only 6 7 per cent of all patients observed with liposarcoma Children with fibrosarcomas and angiosarcomas comprised 10.2 and 10.5 per cent, respectively of all patients bearing these tumors The remainder of the sarcomas in children varied from 2.6 per cent (one patient with dermatofibrosarcoma protuberans) to 8 1 per cent of the total number of sarcomas (see Table

TABLE 89 INCIDENCE OF SARCOMAS OF SOFT SOMATIC TISSUES OF CHILDREN

Histologic Type of Tumor	*Total Cases (All Ages)*	*Patients 15 Years of Age and Less* Number	Per Cent
Total cases	717	51	7 1
Sarcoma of undetermined histogenesis	261	23	8 1
Liposarcoma	105	7	6 7
Rhabdomyosarcoma	100	4	4 0
Synovioma	60	3	5 0
Kaposi s sarcoma	48	0	0 0
Malignant neurilemmoma	46	7	15 2
Fibrosarcoma	39	4	10 3
Dermatofibrosarcoma protuberans	39	1	2 6
Angiosarcoma	19	2	10 5

89) No instance of Kaposi's sarcoma was seen in children

There were certain sarcomas in which the tissue of origin could not be identified and which were therefore labeled "sarcomas of undetermined histogenesis" In the total series there were 261 such unclassifiable sarcomas in all age groups, and of these 23 (8 1 per cent) were in children

Of 24 sarcomas of the soft somatic tissues reported by Andersen from the Babies Hospital in New York, there were 5 fibromas, 3 rhabdomyosarcomas, 2 leiomyosarcomas, 1 embryonal lipoma of low malignancy, 1 malignant hemangiopericytoma, and 12 unclassified sarcomas

Table 89 presents the incidence of sarcomas of infancy and childhood analyzed according to the histologic type of the tumor The data evaluate the relationship of sarcomas which occur in children less than 15 years of age to the total incidence of soft somatic tissue neoplasms occurring in patients of all ages

ATTITUDE TOWARD TREATMENT OF CHILDHOOD CANCER

The attitude toward the treatment of cancer in childhood has evolved through two distinct approaches Most of the early literature implied that no differences existed in the natural history of cancer in childhood and in the adult As increased reports of malignant neoplasms of the very young became available, certain distinguishing characteristics between cancer in the younger individual and cancer in the older individual became apparent For example, the ratio of sarcomas to carcinomas is much greater in children than in adults, and certain organs are the host for cancers in children more frequently than in adults (eye, adrenal cortex, testis, etc) Certain embryonal tumors or teratomas may appear benign histologically but clinically are highly malignant, while others, such as melanomas, in children are usually benign clinically although they may demonstrate a high degree of malignancy by histologic criteria Malignant tumors, as a rule, do seem to grow more readily in the very young without evoking a protective objection by the host

The characteristic of rapid growth with a tendency to early metastasis by many malignant neoplasms in children was responsible for the second attitude regarding the philosophy of treating childhood cancer, namely, one of abject pessimism This pessimistic attitude permeated the profession so that certain physicians refrained from giving any form of treatment, and it infiltrated to the parents who, feeling that the situation was hopeless, would not bring the child with a tumor to the physician

Infants and children tolerate radical operative procedures remarkably well, hence, none should be deprived of the benefits of a surgical attempt at cure So-called inoperability because of frailty of the infant usually reflects a frailty of the surgeon Analysis of the 51 sarcomas of the soft somatic tissues of this series, moreover, reveals that not infrequently a histologically malignant neoplasm will manifest a rather benign clinical course and be subject to cure, whereas in the adult the prognosis would more frequently be fatal In addition, certain tumors in infants and children considered radioresistant on histologic criteria will respond dramatically to irradiation Certain sarcomas in children have been described to revert to a benign status either spontaneously or following irradiation, *e g*, neuroblastoma reverting to a ganglioneuroma

The observation that most sarcomas of the soft somatic tissues in children represent a localized growth originating

usually in a single nidus combined with the fact that 42.1 per cent of all children bearing sarcomas of the soft somatic tissues treated by the authors have survived five years and longer are hopeful signs. It is the distinct impression of the authors that many of the children who delayed long periods or were inadequately treated before referral here could have been cured if adequate treatment had been sought and given with dispatch.

The natural histories of specific sarcomas of this group offer signs for developing the surgical attack upon a given patient. Thus, in patients bearing synovial sarcomas and rhabdomyosarcomas, because of the high incidence of *metastases to lymph nodes every surgical* approach should consider resection of the regional lymph nodes Metastases to lymph nodes have been described for every form of sarcoma. This is contrary *to a common but mistaken impression* that sarcomas metastasize only by way of the blood stream, and it should make the surgeon always consider the possibility of excising en bloc the regional *lymph nodes which drain that anatomic* segment in which the tumor has occurred. This consideration need not be great in such sarcomas as fibrosarcoma or liposarcoma, where metastases to *lymph nodes are rare Because of the* possibility of metastases to lymph nodes the nodes should certainly be excised, especially if the location renders itself suitable to an excision in continuity (See Chap 6)

The therapeutic approaches will vary from a wide surgical excision to the most radical amputation. Irradiation for the most part should not be utilized as the sole method of treating sarcomas If the decision is to treat the patient by wide local surgical excision and postoperative irradiation, the fact that irradiation will be administered after operation should in no way deter the surgeon from effecting the most radical surgical procedure necessary Utilization of an inferior therapeutic modality irradiation, as a crutch for the inadequate application of the superior surgical method of ablating these neoplasms is to be condemned.

Because of the pseudohumane and sentimental considerations which every surgeon must suffer in deciding on a radical extirpation of sarcomas in infants and children, many have yielded *to their emotional impulses and have* performed a limited and conservative excision to avoid surgically mutilating the infant or child. We heartily agree to limited excision where indicated, but *only by a complete understanding of* the behavior patterns of each of the tumors of children can one decide when the excision can be conservative and when it must be radical. In those instances where only the most radical type of surgical resection will offer hope of ablating the cancer fear of mutilation and thoughts of reconstruction must be secondary to the extensive excision necessary to cure the patient. Failure to do this will doom the patient or will necessitate repeated resections with the eventual result that a more radical procedure may be necessary for the treatment of recurrences than would have been indicated for the treatment of the primary neoplasm. The surgeon can for the most part be most conservative by being radical at the outset.

END RESULTS IN TREATMENT OF SARCOMAS OF SOFT SOMATIC TISSUES IN CHILDREN

The end results in the treatment of all sarcomas *of the soft somatic tissues* in infancy and childhood reveal that of the 51 children treated 16 are living, apparently without recurrence, five years and more after treatment, and 8 are liv

Table 90 Five-year End Results in Sarcomas of the Soft Somatic Tissues of Infancy and Childhood

Total cases				51
Indeterminate cases				4
Cases refusing treatment, not completing treatment and lost track of, or treated elsewhere				
Determinate cases			47	
(Entire series)				
Determinate cases			8	
Treated within past 5 years				
Determinate cases		39		
Treated over 5 years ago, used for evaluating five-year cures				
Failures		23		
Died of the sarcoma				
Successful results		16		
Living without evidence of sarcoma five years or more				
5–9 years	6			
10–15 years	4			
15 years or over	6			
Survival rate				

$$\frac{\text{Successful results}}{\text{Determinate cases treated over 5 years ago}} = \frac{16}{39} = 42\ 1 \text{ per cent}$$

ing and apparently without residual sarcoma less than five years after treatment The five-year "cure" rate of all determinate children treated for sarcoma of the soft somatic tissues is 42 1 per cent (Table 90) Twenty-three of the 51 have died as the result of the sarcoma and 4 are listed in the indeterminate group, having been lost to follow-up examinations

Table 91 reveals the curability of all sarcomas in relation to the location of the tumor The over-all mortality equaled 43 1 per cent of the determinate cases The highest mortality occurred in patients who bore sarcomas of the lower extremity, shoulder, and torso, and ranged from 44 4 per cent to 66 6 per cent Patients with sarcoma of the hand apparently enjoyed the best prognosis (none died as the result of the sarcoma), along with those of sarcoma of the arm (66 6 per cent five-year-cure rate of the determinate cases)

Analysis of the end results in relation to the age of the patient reveals that the best prognosis apparently was enjoyed by the nine patients under 1 year of age (Table 92) Only one of these nine succumbed from the sarcoma Three are alive and free of evidence

Table 91 End Results in Relation to Location of Sarcoma of Soft Somatic Tissues of Infancy and Childhood

		Living without Sarcoma				
	Total Cases	*Under 5 Years*	*5 Years and Over*	*Died With Sarcoma*		*Indeterminate Cases*
Location of Tumor	*Number*	*Number*	*Number*	*Number*	*Per Cent*	*Number*
Total cases	51	8	16	22	43 1	5
Hand	2	0	1	0	0 0	1
Arm	13	6	4	2	15 3	1
Shoulder	3	0	1	2	66 6	0
Leg	7	1	1	4	57 1	1
Thigh	9	0	1	4	44 4	1
Back, chest wall, and abdominal wall	17	1	5	10	58 8	1

less than five years after treatment and an additional three are alive and free of evidence five years or longer after treatment. Two are classified as indeterminate because they were lost to follow up The mortality rate for the pa These results should indicate further that malignant neoplasms occurring shortly after birth do not represent an incurable end result of a prenatal disturbance.

A study of the end results in the en

TABLE 92. END RESULTS IN RELATION TO AGE OF PATIENT IN SARCOMA OF SOFT SOMATIC TISSUES OF INFANCY AND CHILDHOOD

		Living without Sarcoma				
	Total Cases	*Under 5 Years*	*5 Years and Over*	*Died With Sarcoma*		*Indeterminate Cases*
Age of Patient	*Number*	*Number*	*Number*	*Number*	*Per Cent*	*Number*
Total cases	51	8	16	22	43 1	5
Under 1 year	9	3	3	1	11 1	2
1–5 years	20	1	8	10	50 0	1
6–10 years	10	1	2	6	60 0	1
11–15 years	12	3	3	5	41 6	1

TABLE 93 END RESULTS IN RELATION TO TYPE OF TREATMENT OF SARCOMAS OF SOFT SOMATIC TISSUES OF INFANCY AND CHILDHOOD

		Living without Sarcoma				
	Total Cases	*Under 5 Years*	*5 Years and Over*	*Died With Sarcoma*		*Indeterminate Cases*
Type of Treatment	*Number*	*Number*	*Number*	*Number*	*Per Cent*	*Number*
Total cases	51	8	16	22	43 1	5
Excision only	11	5*	3	1*	9 1	2
Excision and irradiation	7	0	4	3*	42 8	0
Irradiation only	24	1	8	14†	58 3	1
Amputation	2	0	1	1	50 0	0
Interscapulothoracic amputation	2	2	0	0	0 0	0
Hip-joint disarticulation	1	0	0	1	100 0	0
Hemipelvectomy	1	0	0	1	100 0	0
No treatment	3	0	0	1	33 3	2

In one case treatment was given for palliative purposes only

† In 11 cases treatment was given for palliative purposes only

tients between 1 and 5 years of age is 50 per cent for those between 6 and 10 years of age it is 60 per cent, in the group between 11 and 15 years of age, it is 41 6 per cent. From these data it would appear that the best results can be obtained when the sarcomas are treated in younger subjects.

tire group of children bearing sarcoma of the soft somatic tissues analyzed according to the type of treatment, reveals some rather interesting indices (Table 93) There were 11 patients treated by excision alone of these 5 are apparently free of evidence less than five years and 3 five years or more. The

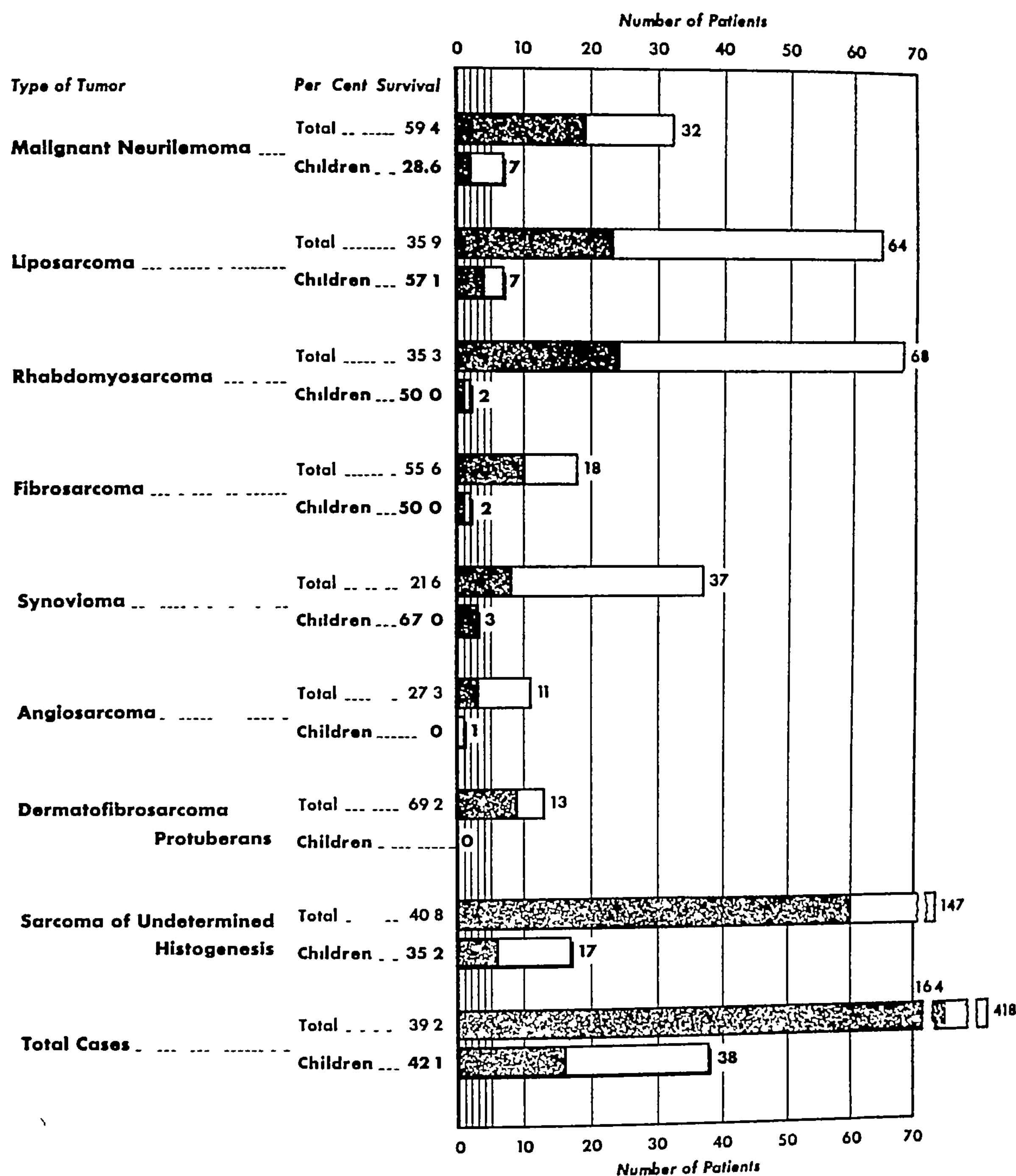


FIG 432 Comparison of survival rates in infancy and childhood with total survival of patients with malignant tumors of the soft somatic tissues (Pack, G T, and I M Ariel Surg Gynec & Obst 98 675, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)

mortality rate in this group is 9 1 per cent Of seven treated by excision plus postoperative irradiation, four are alive and well five years and longer after treatment There were 24 patients treated by irradiation alone, of whom 11 were given irradiation for palliative purposes only Eight additional patients treated by irradiation are alive and apparently free of sarcoma over five years after treatment There were two patients treated by amputation and one is well over five years and the other is dead Two patients were treated by interscapulothoracic amputation and they are both well, but the elapsed time is less than five years so final evaluation must await further follow-up One patient who was treated by hip-joint disarticulation died, and another was unsuccessfully treated by hemipelvectomy

These data in no way reflect the efficacy of a given modality for curing sarcoma because the more radical measures

were utilized for the more extensive neoplasms. These data do demonstrate that cures can be obtained. Continued critical evaluation will determine the proper combination of treatment methods that should be applied to a given child with a sarcoma of the soft somatic tissues

END RESULTS ANALYZED ACCORDING TO HISTOLOGIC TYPE OF SARCOMA

The five-year-cure rates following *treatment of soft somatic tissue sarcomas* are presented in Table 90

The over-all five-year-cure rate for the 39 determinate infants and children is 42.1 per cent, which is slightly better than the 39.2 per cent for the over-all series of 418 determinate patients of all ages with sarcomas Thus sarcomas of supporting structures in infants and children can be treated as successfully as if not more successfully than their congeners in the adult. The specific sarcoma that reacted most satisfactorily to treatment was the malignant synovioma, with a survival rate of 66 7 per cent. This value is in sharp contrast to the five-year survival of 21 6 per cent of patients of all ages bearing synovial sarcomas Children with liposarcoma revealed a 57 1 per cent five-year survival and those with rhabdomyosarcoma and fibrosarcoma each enjoyed a 50 per cent five-year-cure rate.

Young patients with sarcomas of undetermined histogenesis—usually a malignant variety of tumor—showed a 35.2 per cent five-year survival. Patients with malignant neurilemmoma had a 28 6 per cent survival rate and the one child with angiosarcoma succumbed to the tumor Figure 432 shows the total experience of patients of all ages bearing soft somatic tissue sarcomas compared with that of the juvenile human under 15 years of age. It may be noted that the end results in the infants and children compare favorably with the over-all prognosis

In certain groups a betterment of results is noted in sarcomas of childhood (synovioma, 66 7 per cent survival rate in children versus 21.6 per cent for adults) In no group was the end result in the lower age brackets significantly poorer than in adults

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SECTION V

Regional Anatomic Considerations in the Treatment of Tumors of the Soft Somatic Tissues

Most tumors of the soft somatic tissues occur in the extremities Principles for their treatment are discussed in Chapters 7 to 14 In certain instances, such as of tumors of the neck, the anatomy and surgical technics constitute a surgical sphere that is beyond the scope of this volume. Accordingly, data are presented in Chapter 26 pertaining to the incidence and types of tumors most frequently encountered in the neck Tumors of the anterior abdominal wall are discussed in Chapter 27 as regards their incidence, histologic types, and the position of tumors arising from the soft somatic tissues in relation to all tumors and tumorlike proliferations in this anatomic region Neoplasms arising from the retroperitoneum and the buttocks present special therapeutic problems that are considered in Chapters 28 and 29, respectively

CHAPTER 26

Soft Somatic Tissue Tumors in the Neck

INTRODUCTION

The neck of man is a relatively small structure, averaging about 10 cm. in length and 25 cm in diameter Concentrated in this relatively small region are numerous structures, each of which may give rise to tumors. Most malignant neoplasms of the cervical region are metastatic carcinomas Primary neoplasms of the neck structures are relatively rare (exclusive of those which occur in cervical organs thyroid gland, etc.) The most frequent primary cervical cancers are those which arise from the lymph nodes (lymphomas) Of 304 malignant

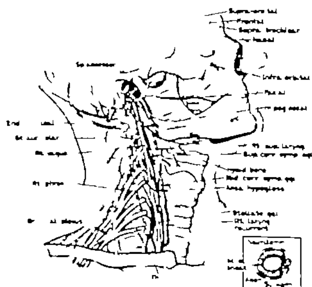


Fig. 433. Nerve elements of neck, showing various potentials for the development of tumors. (*Courtesy* Dr John J Conley and A.M.A. Arch. Otolaryng. *61* 167 1955)

neoplasms reported by Mayo and Lee, 103 (34 per cent) were metastatic carcinoma to the cervical lymph nodes and

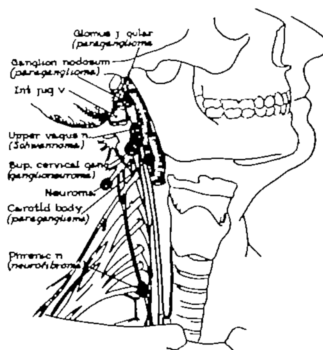


Fig. 434. Tumors of neurogenous origin occurring in the neck and the relative positions in which the tumors are most commonly encountered. (*Courtesy* Dr John J Conley and A.M.A. Arch. Otolaryng *61* 167 1955)

69 (22 per cent) were lymphoblastomas Only one sarcoma was encountered, this was a fibrosarcoma. In the same series there were 305 benign lesions as follows 35 keratoses 31 lipomas 30 thyroglossal-duct cysts 17 parathyroid tumors, 13 branchial-duct cysts 6 ade-

nocytomata lymphomatosa, 6 neurofibromas, and 25 miscellaneous growths These findings agree with those of others Martin and Morfit have demonstrated that the most common cause of cervical lymphadenopathy in the adult is metastatic carcinoma, usually from intraoral cancers, and that the tumor of the neck was a first symptom in 7 8 per cent of 1,867 patients with intraoral cancers

Tumors arising in the soft somatic tissues of the neck constitute a small percentage of all cervical neoplasms Practically every type of benign and malignant tumor occurring in the soft somatic tissues has been described in this location The most frequent group are those arising from the numerous nerves in this region

Although certain benign neoplasms, such as hemangiomas, occur in the cervical structures with a frequency in proportion to the volume of tissue, sarcomas are seldom encountered in the neck. Their treatment demands an intimate knowledge of the surgical anatomy of the region, including the relationships of the various triangles of the neck, the distribution of the cervical lymph nodes (for the performance of a neck dissection when indicated), and the distribution of the different nerves in this location

BENIGN TUMORS OF SOFT SOMATIC TISSUES

Benign tumors occur not infrequently in the neck Such tumors of soft somatic tissue as *hemangioma and lymphangioma* (in which group is included the well-known hygroma coli) are treated similarly to such tumors elsewhere (Chap 19) The position in the neck usually does not present any specific therapeutic problem Hemangiomas of the Sturge-Weber's syndrome often extend from the face down to the neck and are associated with intracranial disturbances (page 416)

In the treatment of *cervical lipomas* the therapeutic considerations depend on the location If superficial, they are simply enucleated Often, however, a lipoma may arise inferior to the deep fascia and sternocleidomastoid muscle The therapeutic problems involve exposure through these structures and operative manipulation in close proximity to such vital structures as the common carotid artery, jugular vein, etc Accordingly it becomes essential to differentiate between the superficial and deep lipomas in planning the therapeutic attack and to assure adequate exposure for the latter.

Congenital sternocleidomastoid tumor (congenital muscular torticollis) is discussed in Chapter 15

TUMORS OF NERVES*

The abundant nerves within the neck often give rise to tumors (see Chap. 23)

The Schwann cell is the one responsible for the majority of tumors of neurogenous origin in the neck Its benign neoplastic growth can occur in any nerve fiber possessing a neurilemma This includes the cranial nerves and sympathetic systems in the neck

The ganglion cells of the sympathetic nervous system in the neck present varying degrees of differentiation from the mature benign cell of the ganglioneuroma through the partially differentiated ganglioneuroma to the malignant neuroblastoma (sympathicoblastoma

* From J J Conley A M A Arch Otolaryng *61* 167, 1955



FIG. 435 Preoperative and postoperative photographs of recurrent fibrosarcoma of the neck treated by radical neck dissection, claviculectomy and skin grafting

Tumors arising from such specialized paraganglionic structures as the carotid body and glomus jugulare are presented according to their histologic nosology in Chapter 23.

NEUROMAS

Neuromas occur after amputation of the nerve element or after trauma to a nerve. The phenomenon is rare from the clinical point of view when one considers the large number of nerves severed during a radical neck dissection. Nature's efforts to reconstitute the nerve pathway by regeneration of the Schwann cells and mesodermal elements in the cervical nerves are frustrated because of the absence of any distal nerve elements with which to form union and continuity This nonneoplastic proliferation of neurectoderm forms a fusiform type of bulbous enlargement of the proximal nerve segments into which new axis cylinders grow They become entangled in the proliferated Schwann cells and mesodermal elements and scar tissue If the regenerative process is not overly active and the scar tissue not hypertrophic in character the perception of pain or discomfort in the area of this transected nerve never reaches the clinical level. However if the proliferative procedure is hyperactive and the scar tissue is excessive, the patient will complain of localized pain and tenderness It rarely reaches excruciating proportions There is a responsibility in differentiating the occurrence of this *new mass from the original neoplasm* that necessitated the radical neck dissection

TREATMENT

The treatment of amputation neuroma of the neck is never urgent, and indeed, temporization may lead to spontaneous improvement. This is particularly true if the neuroma appears within the first year after surgery and is associated with excessive scar formation in the wound. After an interval of a year a *considerable amount* of the scar tissue disappears spontaneously and there is often marked relief of the discomfort in the neck. If however the symptoms persist into the second year and a localized and painful and tender mass is present in the region of the stumps of the cervical nerve elements the neuroma should be excised.



FIG 436 (*Left*) Schwannoma arising from neurilemma of vagus nerve (*Right*) Schwannoma bulging into nasopharynx (*Courtesy*, Dr John J Conley and A M A Arch Otolaryng *61* 167, 1955)

NEURILEMMOMA (SCHWANNOMA)

Schwannomas of the fifth, seventh, eighth, and tenth cranial nerves, phrenic nerve, cervical and brachial plexuses, and cervical sympathetic nerves have been described

The tumor enlarges slowly, attaining a size of from 1 to 7 cm over a period of years The tumor usually causes no symptoms Pain is absent, and the patient merely relates his awareness of the tumor mass If the tumor mass becomes unusually large and is situated in a vital functioning area or in a vital position in the nerve trunk, it may cause interference with breathing, swallowing, talking, and moving the head, and may be associated with pain and paresthesia The course is benign throughout, and malignant change has not been reported

TREATMENT

Treatment is always total surgical removal The tumors are encapsulated and do not metastasize They are not sensitive to radiation During the operation every effort should be made to conserve the continuity of the neural pathway, as the tumor is essentially an encapsulated benign tumor of the neural sheath A normal noninvolved segment of the nerve should be identified on each side of the neurilemmoma and traced to the tumor The nerve may have been pushed to one side by the development of the tumor, or it may have become spread out as a result of the growth of the tumor and its capsule between the different nerve fasciculi

In the vast majority of instances, care in the isolation of the nerve while the tumor is being removed will preserve the continuity of the neural bundle If it is technically impossible to preserve the nerve bundle intact and the tumor is less than 2 cm in length, it may be possible to do a direct end-to-end approximation of the cut nerve ends after appropriate mobilization of the proximal and distal nerve segments, and angulation of the head and neck to relieve tension on the suture lines If it is necessary to excise more than 2 cm of the nerve and this pathway has vital clinical significance, one should consider the immediate implantation of a free nerve graft

The surgical treatment of malignant neurilemmomas is discussed in Chapter 23

GANGLIONEUROMA

Any of the cervical sympathetic ganglia of the neck may be involved by this tumor growth It is found predominantly in children in adolescence with a slight

preponderance in females It is uncommon. The tumor is encapsulated it does not infiltrate and does not metastasize It may attain a large size, however and, as the result of pressure may grow through one of the intervertebral foramina and continue to expand in the spinal canal.

When these tumors originate in one of the cervical sympathetic ganglia of the neck, a Horner s syndrome is usually present. The patient has no specific group of symptoms when the tumor is small, other than the awareness of the presence of this tumorous mass As the tumor increases in size a pressure phenomenon affecting the local area and other associated nerves may manifest itself in progressive difficulty in speaking, breathing, swallowing, or moving the head. The size of the tumors may be of such magnitude as to cause asphyxiation and starvation, and if they have entered the spinal canal, paraplegia may develop

TREATMENT

The treatment of this condition is complete surgical removal. The tumors are insensitive to radiation The surgical extirpation of this tumor means resection of a portion of the sympathetic chain. If the tumor is small, the other associated nerves in the locality of the tumor may not be entrapped by its growth, and will therefore, not necessarily have to be resected. If however it becomes encapsulated and enmeshed with these nerves it may be necessary to resect them along with the tumor mass The nerves which are most frequently involved are the vagus spinal accessory hypoglossal, and cervical plexus If it is necessary to sacrifice these additional associated nerves then end to-end approximation and free nerve grafts should be carried out during the operation. The prognosis is excellent.

MALIGNANT TUMORS

Malignant tumors of the soft somatic tissues of the neck comprise less than 0.5 per cent of all tumors of the soft somatic tissues Those arising from soft somatic structures other than the nerves are extremely rare, and sufficient data are not available to permit a comprehensive analysis regarding their natural history and the end results of treatment. Each tumor must be individualized in planning the therapeutic attack, depending upon the histologic type and the involved anatomy

SYMPATHICOBLASTOMA (NEUROBLASTOMA)

The highly malignant sympathicoblastoma is very rare in the neck (see case report No 70) When it occurs in the sympathetic cervical ganglion it grows rapidly infiltrates all the surrounding tissues increases in size at the destructive expense of its neighbors, and metastasizes freely by all routes, particularly through the blood stream. (Chap 23)

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CHAPTER 27

Soft Somatic Tissue Tumors of the Abdominal Wall*

The literature contains no comprehensive reports which deal specifically with tumors of all varieties limited to the anterior abdominal wall or with diseases of the abdominal wall in general, except for Cullen's classic monograph on diseases of the umbilicus and von Klot's review of collected cases of tumors of the abdominal wall published in 1921.

Whereas amputation may finally be resorted to for a malignant growth on one of the limbs radical excision of an appreciable segment of the anterior abdominal wall, followed by the necessary reparative plastic procedures provides situations of unusual surgical difficulty Also standard technics in radiation therapy must be altered in treating tumors of the anterior abdominal wall because of the highly vulnerable underlying intestines and ovaries The anterior abdominal wall may well be considered as a *surgical organ* because of these peculiar problems in addition to the well-recognized importance of this anatomic structure in the study of umbilical and inguinal hernias and the healing of laparotomy wounds

The present report is based on an analysis of 470 tumefactions in this locality and includes 391 cases of neoplasia. Only those cases have been considered in which tissue was available for microscopic examination (except for hemangioma of the skin) and where the follow up data were adequate Tumors which were located below Poupart's ligament, *i.e.*, situated entirely within the groin, were omitted from this study

SURGICAL ANATOMY

Topographically the anterior abdominal wall is bounded above by the flare of the costal margins and the xiphoid process of the sternum and below by the iliac crests inguinal ligaments, pubic crests and pubic symphysis The large flat muscles should be regarded as the anterior abdominal wall leaving the posterior abdominal wall as that portion composed of the psoas major and minor quadratus lumborum, and iliacus muscles The principal structures that comprise the anterior abdominal wall are the recti, external and internal oblique, transversalis, piriformis and lower intercostal muscles together with their enveloping fascial sheaths and aponeuroses.

The blood supply is furnished by the

* In collaboration with Harry E. Ehrlich

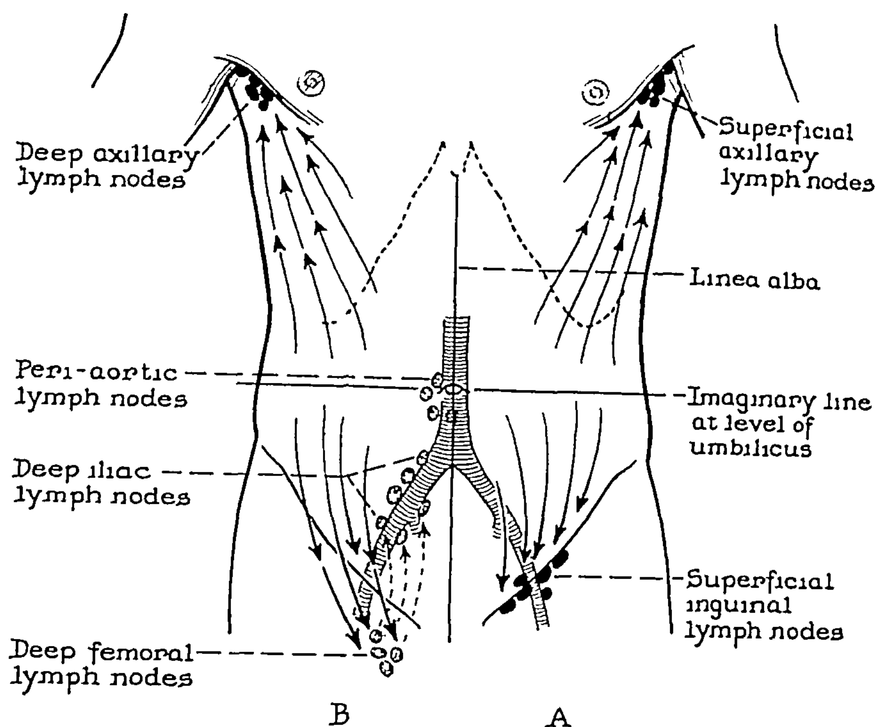


FIG 437 Diagram of the lymphatic drainage (of surgical importance) of the anterior abdominal wall *A* Superficial lymphatic system *B* Deep lymphatic system (Pack and Ehrlich, Surg Gynec & Obst *79* 177, 1944 (*Courtesy,* Surgery, Gynecology and Obstetrics)

superior and inferior mesenteric, internal mammary, lower two intercostal, lumbar, iliolumbar, and circumflex iliac arteries Venous drainage above the umbilicus is into the superior vena cava, below the umbilicus into the inferior vena cava, and from the umbilicus into the portal circulatory system via the veins of the round ligament of the liver

The superficial lymphatic vessels of the upper anterior abdominal wall drain into the superficial axillary lymph nodes, and those of the lower anterior abdominal wall empty into the superficial inguinal nodes The deep lymphatics of the upper anterior abdominal wall run to the deep axillary lymph nodes, those of the lower anterior abdominal wall drain into the deep femoral group via the inferior epigastric and deep circumflex iliac trunks, and into the periaortic nodes through the lymphatics which accompany the lumbar arteries and veins (Fig 437)

The umbilicus is of particular surgical interest because of its relation to the portal circulation and the liver, peritoneal cavity, urinary bladder, and anterior mediastinum, in addition to its embryonic rudimentary structures (umbilical ligaments) The superficial lymphatics of the umbilical ring empty into the superficial axillary and inguinal lymph nodes The deep lymphatics of the umbilical ring run to the deep axillary, the anterior mediastinal (via the internal mammary trunks), the deep femoral (via the inferior epigastric trunks), and the periaortic lymph nodes (via the lymphatics which accompany the lumbar vessels) The lymph flow may also be directed to the deep iliac group from the deep femoral lymph nodes Still other lymphatics ascend along the ligamentum teres (obliterated umbilical vein) to reach the porta hepatis (Fig 438) The lymphatics of the urinary bladder anastomose with the lymphatics of the umbilicus via the vestigial urachal structures

Lymph nodes are largely confined to the deeper fascial planes, recti muscles, and the periumbilical preperitoneal tissues They are not major groups, but are

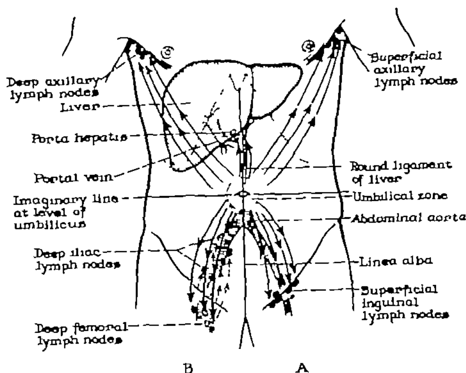


FIG. 438. Diagram of the lymphatic drainage (of surgical importance) of the umbilical zone. A. Superficial lymphatic system. B Deep lymphatic system. (Pack and Ehrlich, Surg. Gynec. & Obst. 79 177 1944. *Courtesy* Surgery Gynecology and Obstetrics.)

small intercalated nodes scattered along the lymphatic pathways.

The linea alba, a tendinous raphe which stretches down the middle of the anterior abdominal wall between the xiphoid process and the symphysis pubis is formed by the blending of the aponeuroses of the oblique and transversalis muscles As this dense fascial band is not perforated by lymphatic capillaries it partitions the deep lymphatic system of the anterior abdominal wall into right and left halves, so that cross metastases of intramural tumors occur only when a malignant growth is situated behind the transversalis fascia or the posterior rectus sheath, *i.e* in the preperitoneal fatty areolar layer—a most unlikely location for a primary lymphatic-metastasizing neoplasm There are, however sufficient lymphatic anastomoses at all levels in the umbilical zone so that bilateral or even quadrilateral regional lymph node metastases may occur from a primary malignant tumor in this central area.

BENIGN TUMORS

There were 242 benign tumors (51.5 per cent) in our series, constituting the largest group (Table 94) Of the 305 primary neoplasms 80 per cent were benign and 20 per cent were malignant. The sexes were almost equally affected (130 males and 112 females) The ages varied from 6 weeks to 77 years at the time of admission and the average age was 33

Thirteen distinct morphologic types of tumors were encountered (Table 95) The common benign neoplasms in order of their frequency were lipomas neuronevi hemangiomas epithelial papilliomas, fibromas, neurofibromas and keratoses or keratotic papillomas. Lipomas are the most common of all tumors in addition to being the most frequently occurring benign tumor (20 per cent) in the anterior abdominal wall. Benign tumors which may occu

TABLE 94 TUMEFACTIONS OF ALL KINDS IN THE ANTERIOR ABDOMINAL WALL

Type of Tumor	Cases		Per Cent	
Total		470		100 0
Neoplastic		391		83 2
Benign tumors	242		51 5	
Primary malignant tumors	63		13 4	
Metastatic malignant tumors	64		13 6	
Malignant lymphomas	22		4 7	
Nonneoplastic		79		16 8
Cysts	24		5 1	
Tumefactions inflammatory in origin	31		6 6	
Miscellaneous lesions simulating tumors	24		5 1	

sionally offer difficulties in management are nevus unius lateralis, extensive neurofibromas of the von Recklinghausen type, desmoid tumors, and lymphangiomas

TABLE 95 BENIGN TUMORS OF THE ANTERIOR ABDOMINAL WALL

Morphologic Type	Cases	Per Cent
Total	242	100 0
Lipoma	48	19 8
Neuronevus	41	16 9
Hemangioma	33	13 6
Epithelial papilloma	29	20 0
Fibroma	22	9 1
Neurofibroma	22	9 1
Keratosis or keratotic papilloma	20	8 3
Desmoid tumor	17	7 0
Lymphangioma	4	1 7
Dermatomyoma	2	0 8
Schwannoma	2	0 8
Sweat-gland adenoma	1	0 4
Xanthofibroma (perithelial)	1	0 4

Desmomas (desmoid tumors) are benign neoplasms which often infiltrate extensively the abdominal wall and occur most frequently in females following pregnancy Although benign histologically, they may be clinically malignant by virtue of their extensive infiltrations (see case report No 7) These neoplasms tend to be indigenous in the abdominal wall, although they occasionally occur in other locations Desmomas and the uncommon desmoid tumors of children are discussed at length in Chapter 15

The management of nevus unius lateralis or neuropathic papilloma (Pack and Sunderland) consists of complete surgical excision of the entire thickness of the involved epidermis, occasionally in multiple stages Plastic repair is usually necessary, either by skin grafting or by undermining the skin sufficiently to effect primary wound closure by sliding flaps It is essential that no tumor tissue be left behind, for this neoplasm is not infrequently subject to malignant changes.

There were 22 neurofibromas in this series, and of these 13 were of the von Recklinghausen type The solitary encapsulated neurofibroma is usually located subcutaneously and is enucleated with ease The plexiform von Recklinghausen type, however, is frequently extensive, multiple, and infiltrating, requiring for its complete removal wide dissection, occasionally in multiple stages The policy of radical excision of the neurogenic tumors, especially in patients afflicted with von Recklinghausen's multiple neurofibromatosis, is based on the observation that this type of neurogenic tumor occasionally undergoes malignant transformation Case report No 78 illustrates

the difficulties and complications which are sometimes encountered in the surgical management of such a neoplasm.

Neurofibromas may rarely be located both *intramurally and intraperitoneally* Such a situation presents unusual diagnostic difficulties even during surgical exploration, as shown in case report No 79

In the *vascular group* there were 33 hemangiomas and 4 lymphangiomas Treatment differed in no way from the treatment of hemangiomas described in Chapter 19 (See case report No 80)

PRIMARY MALIGNANT TUMORS

There were 63 primary malignant tumors in the present series These represent 13 4 per cent of all tumefactions 16 1 per cent of all true neoplasms and 42.3 per cent of all malignant tumors in the anterior abdominal wall. It can be seen from Table 94 that primary and metastatic tumors occur with about equal frequency in this locality This is *in sharp contrast with the incidence of* similar lesions in the soft parts elsewhere, particularly on the limbs, where metastatic malignant tumors are distinctly uncommon. The multiplicity of lymphatic and venous connections, especially with the peritoneal cavity and *portal circulation through the umbilicus* makes the anterior abdominal wall particularly vulnerable to secondary cancerous deposits and explains for the most part the relatively high incidence of metastases in this structure.

The incidence, histologic types, and *clinical features of carcinomas* are briefly presented for purposes of comparison.

Of 63 primary malignant neoplasms 25 were tumors of epithelial origin carcinomas represent 6 4 per cent of all neoplasms and 16 8 per cent of all malignant tumors primary and secondary *in the anterior abdominal wall.* There were 14 females and 11 males in this group The ages varied from 36 to 74 years at the time of admission and the average age was 52 years. They were classified into three general groups—epidermoid carcinomas, basal-cell carcinomas and *adenocarcinomas* (Table 96)

Primary carcinoma in the skin of the anterior abdominal wall is relatively uncommon when compared with its occurrence in other parts of the body Furthermore, in other locations malignant tumors of connective tissue origin are much less frequently encountered than are malignant epithelial tumors (ratio 5 1) while carcinomas and sarcomas in the *anterior* abdominal wall occur with about equal frequency The greater protection afforded the skin of the anterior abdominal wall accounts in a good measure for the relative infrequency of carcinoma in this locality

TABLE 96 PRIMARY MALIGNANT TUMORS OF THE ANTERIOR ABDOMINAL WALL

Type of Tumor		*Cases*
Total		63
Carcinoma (39 7 per cent)		25
Epidermoid carcinoma	17	
Basal-cell epithelioma	6	
Adenocarcinoma	2	
Sarcoma (47 6 per cent)		30
Malignant neurilemmoma	9	
Spindle-cell sarcoma	8	
Synovioma	5	
Rhabdomyosarcoma	4	
Dermatomyosarcoma	2	
Liposarcoma	1	
Granulation-tissue sarcoma	1	
Melanoma (12.7 per cent)		8

It is highly significant that of 17 cases of epidermoid carcinoma, 2 were engrafted on demonstrable preexisting tissue abnormalities.

SARCOMA

Primary sarcomas are more frequently found in the anterior abdominal wall than primary carcinomas There were 30 primary malignant tumors of connective-tissue origin in this series of 391 neoplasms of the anterior abdominal wall, making an incidence of 7 7 per cent They comprise 20 1 per cent of all malignant tumors and 47 6 per cent of all primary malignant tumors in this location Their number would be increased if those desmoid tumors which have undergone malignant transformation into fascial fibrosarcomas were included in this group, but this unique neoplasm, a clinicopathologic entity, has been considered separately

Seven distinct morphologic types were encountered (see Table 96) The most common tumors in order of frequency were malignant neurilemmomas, spindle-cell sarcomas (unclassified), synoviomas, and rhabdomyosarcomas Occurring more rarely in this region were dermatomyosarcomas, liposarcomas, and granulation-tissue sarcomas (See case report No 81) The diagnosis was established by aspiration biopsy in about three-fourths of the cases

There were no common causative factors The sexes were equally affected and the ages varied from 19 to 61 years at the time of admission, with an average age of 34 years It will be noted that these patients are considerably younger than those in the group with carcinoma Only among the neurogenic tumors could any significant etiologic factors be established Of 9 cases of neurilemmoma 5 were secondary to von Recklinghausen's neurofibromatosis and 1 originated in a laparotomy scar

As the majority of sarcomas arise in the deeper layers of the abdominal wall, they have usually reached considerable proportions by the time they are first noted by the patient or the physician The treatment of these tumors must consist of a wide resection of a full-thickness segment of anterior abdominal wall, including the underlying parietal peritoneum

METASTATIC MALIGNANT TUMORS

Primary and secondary malignant tumors occur with about equal frequency in the anterior abdominal wall (see Table 94) There were 64 cases of metastatic and implantation cancers in this series They comprise 16 4 per cent of all neoplasms and 42 9 per cent of all malignant neoplasms in this locality. Their incidence is probably much higher than our figures indicate Frequently, the primary source has been established by the time secondary deposits appear, obviating need for a biopsy, and only those cases were included in this study in which tissue was available for microscopic examination The number of cases would be further increased if malignant lymphomas were also to be considered in this group

The great majority of metastatic neoplasms in the anterior abdominal wall were carcinomas (84 4 per cent) The remainder consist of sarcomas, melanomas, and rare miscellaneous malignant tumors

The presence of a metastatic cancer nodule in the anterior abdominal wall is a grave prognostic omen This has been emphasized by Cullen No patient in this group who harbored one or more such deposits secondary to malignant tumors somewhere in the peritoneal cavity survived more than 6 months and no patient in the entire series (except for implantation cancer) survived more than 10 months

IMPLANTATION CANCER

The eight cases of implantation cancer occurred secondary to operations for malignant tumors on the urinary bladder

(3 cases) uterus (2 cases) ovary stomach, and large bowel. In contrast to the appalling mortality of cancers secondary to chronic draining abdominal sinuses, the mortality in this group was 50 per cent, and these patients succumbed to the primary uncontrolled tumor, recurrences or widespread metastases, but not as a result of the tumor implant in the abdominal scar. In further contrast to cancers secondary to chronic draining abdominal sinuses implantation cancers do not invade the peritoneal cavity. They may however metastasize to the regional lymph nodes. If the primary tumor has been adequately eradicated, the prognosis remains favorable for cases of implantation carcinoma, or sarcoma.

MALIGNANT LYMPHOMA

These tumors occur in the anterior abdominal wall far more often than is suspected. In most instances the disease is either widespread or the diagnosis is firmly established by the time they appear in this soft somatic tissue structure. In 22 cases however the first indication of lymphosarcoma, Hodgkin's disease, leukemia, or mycosis fungoides was tumefaction in the anterior abdominal wall. This is a rare initial manifestation of the lymphomatoid diseases, since during the period 1917 through 1943 more than 1100 cases of malignant lymphoma were seen at the Memorial Hospital. The lesions varied from a shotty subcutaneous nodule to bulky intramural masses. In all cases further investigation revealed lymphomatoid disease affecting other tissues or organs. Malignant lymphomas are mentioned merely for reasons of differential diagnosis. The correct diagnosis may only be made by histologic studies of material obtained from the tumor.

MISCELLANEOUS LESIONS SIMULATING TUMORS IN THE ANTERIOR ABDOMINAL WALL

Not infrequently a nonneoplastic process produces tumefaction in the anterior abdominal wall which may simulate true neoplasia. Such a process may be cystic, specific inflammatory nonspecific inflammatory degenerative, or traumatic in nature. There were 79 cases of this type in our series. They comprise 16.8 per cent of tumefactions in this location.

The most common nonneoplastic lesions are cysts (sebaceous urachal, and sweat gland) and chronic nonspecific inflammatory masses. Less often encountered are nonmalignant radiation ulcers, fat necrosis tuberculosis and endometriosis. There were two cases of Boeck's sarcoid and one instance of spontaneous hematoma in a female patient.

Aspiration biopsy should be of special value in this group of nonneoplastic lesions. Many of them do not require surgical management, and an established anatomic diagnosis would enable the surgeon to proceed with a more conservative plan of treatment.

Nonspecific chronic inflammatory tumors and tuberculosis in the tissues of the anterior abdominal wall are of interest to the oncologist particularly from the point of view of differential diagnosis. They have been adequately described by Namikawa and Sugai. Umbilical endometriosis and endometriosis in laparotomy scars have the same significance for the tumor therapist. Comprehensive reports dealing with endometriosis of the abdominal wall have been published by Pratt, Maes, Schauffler Masson, and others. Hydatid cysts in the anterior abdominal wall (described by Adams Gowland, Negrie and Rolland, and Lanos) and dermoid cysts (reported by W J Taylor Rispal and de Verbizier and Schwarz) were not encountered in the present series. Unusual le-

sions in the anterior abdominal wall, like fungous tumors (Philips) or Schloffer's tumor, were not seen

There was, however, one case of spontaneous hematoma in a female patient. This rare interesting syndrome has been described by Wiener, Taylor, Fothergill, and Maxwell It occurs in young women, frequently during or shortly following pregnancy There is usually no preceding history of trauma In most instances the tumefaction develops slowly, but may appear suddenly and may even simulate an acute intraabdominal episode Such lesions are invariably situated in the lower anterior abdominal wall beneath the deep fascia and may attain considerable proportions This tumefaction is frequently mistaken for a desmoid tumor because of its location and its relation to pregnancy The etiology is obscure Treatment consists of incision and evacuation of the hematoma

Our case was unique in that the overlying skin contained a moderate-sized nevus unius lateralis (neuropathic papilloma) The hematoma was drained through an incision well below the site of the skin tumor, which was simultaneously excised

TUMORS OF THE ANTERIOR ABDOMINAL WALL: CASE REPORTS

CASE REPORT NO 78
NEUROFIBROMATOSIS

R S, a white, male child, age 7, was first seen at the Memorial Hospital on October 10, 1934, for a congenital tumor of the abdominal wall There was no familial history of multiple neurofibromatosis The patient, however, presented stigmas of von Recklinghausen's neurofibromotosis—café-au-lait pigmentation of the skin and skeletal deformity, characterized by lordosis, scoliosis, and stunted growth Examination revealed a soft compressible tumor, involving the right anterior and posterior abdominal walls and extending from the vertebral column to the umbilicus and from the eleventh rib to the iliac crest The mass measured approximately 22 × 14 cm Numerous hard nodules, varying from 1 to 4 cm in diameter, were scattered throughout the tumor

First Operation (October 12, 1934)

A generous portion of the skin which contained multiple neuromas was excised, after which skin flaps were developed from the level of the seventh thoracic vertebra to the iliac crest The entire tumor, including the underlying lumbodorsal fascia and the fascia covering the adjacent external oblique and latissimus dorsi muscles, together with the subcutaneous tissues from the level of the seventh to the level of the tenth thoracic nerves, was dissected out en masse

Second Operation (August 30, 1939, for Recurrent Plexiform Neuroma)

The old scar, including a generous skin ellipse, was excised, and a wide dissection was carried out for the subcutaneous nodular tumor which extended from the right lower ribs to the crest of the ilium and the inguinal ligament and from the vertebral column to the midline of the anterior abdominal wall Convalescence was uneventful

Third Operation (June 28, 1941, for Recurrent Plexiform Neuroma)

A Y-shaped incision was made from the angle of the right scapula around to the lower anterior pectoral fold and down to the iliac crest The tumor was situated beneath the lumbodorsal fascia and the external oblique muscle It was multilobulated, infiltrative, and contained a myriad of budding processes The growth had to be dissected from the retroperitoneal space, perirenal fat, and parietal pleura

Fourth Operation (June 5 1943 for Recurrent Plexiform Neuroma)

An oblique incision, 10 cm in length, was made above and parallel to Poupart's ligament. Skin flaps were prepared superiorly to the level of the right costal margin and inferiorly to the inguinal ligament. The dissection was carried down to the sacrospinalis and external oblique muscles and the tumor was excised en bloc.

Convalescence was stormy and protracted, because of a wound infection (*Staphylococcus aureus hemolyticus*)

Comment

This case illustrates how invasive a plexiform neurofibroma of the von Recklinghausen type may be and the repeated formidable surgical procedures often necessary to effect a cure. It also shows how stubbornly recurrent these tumors may be in spite of adequate, radical surgical excision.

CASE REPORT NO 79: NEUROFIBROMA OF THE LIGAMENTUM TERES

A. L. a 55-year-old, white married female, was admitted to the Memorial Hospital on June 22 1933 for episodes of pain in the right upper abdominal quadrant, nausea and vomiting of 9 years duration, occurring every two to three months. In January 1929 a laparotomy had been performed at another hospital through an upper right rectus incision A hard mass was removed from the colon which proved to be a fecolith No other abnormalities were apparently noted by the surgeon at this time The attacks of abdominal pain continued and 4 years later the patient was able to palpate an abdominal tumor

Physical examination revealed a well healed scar in the upper right rectus. Just to the right of the midline and midway between the xiphoid process and the umbilicus was a round, hard mass, measuring 7 cm in its greatest diameter It was slightly mobile not attached to the abdominal scar and appeared to be located intramurally Fluoroscopic and x ray studies of the gastrointestinal and biliary tracts revealed no evidence of any intrinsic lesions or calculi. Aspiration biopsy of the tumor did not yield tissue sufficiently characteristic for histologic diagnosis.

Operation

The previous scar was excised and an encapsulated, hard tumor 4 cm in greatest diameter was encountered in the subcutaneous tissues. This tumor was continuous with a mass, 10 cm in greatest diameter lying beneath the parietal peritoneum The more superficial and smaller portion of the tumor was located intramurally and the larger portion was located intraperitoneally The intraabdominal part of the tumor was adherent to the omentum The mass was first freed from the adjacent fascia and muscles and, as the dissection was carried down to the abdominal cavity it was observed that the neoplasm arose from the round ligament of the liver The intraperitoneal growth was dissected out from the peritoneal leaves of the falciform ligament the adherent omentum was separated from the tumor and the mass was removed in toto The abdomen was closed in layers

The postoperative course was uneventful and the patient remained symptom free

Microscopic examination of the surgical specimen revealed the usual structure of a neurofibroma

Comment

Failure to identify an intramural tumor may in part be due to rapid incision of the abdominal wall, followed by immediate retraction of the parietes especially if a tumor is not suspected in this location.

CASE REPORT NO 80: LYMPHANGIOMA

L. W a 15-year-old, white male was admitted to the Memorial Hospital on July 6 1939 for a tumor of the lower anterior abdominal wall and right groin first noted at the age of 3 Examination revealed an irregularly globular soft faintly purplish mass which occupied the right lower abdominal quadrant and extended below



FIG 439 An extensive lymphangioma in the lower anterior abdominal wall and groin which was removed in a one-stage operation (Case report No 80) (Pack and Ehrlich, Surg Gynec & Obst 79 177, 1944 *Courtesy*, Surgery, Gynecology and Obstetrics)

Poupart's ligament It was situated intramurally and measured 20 cm in greatest diameter (Fig 439)

Operation

A linear incision was made beginning on the anterior aspect of the right thigh at the junction of the middle and upper thirds and was continued upward on the anterior abdominal wall to the level of the umbilicus Skin flaps were developed Lymphangiomatous tissue involved the deeper layers of the skin in some places, so that the flaps had to be made extremely thin After considerable dissection, the mass was completely circumscribed from the umbilicus to a point 7 cm below the femoral trigone and from the corresponding pubic spine to a point over the greater trochanter of the femur The incision was continued down to the fascia of the external oblique muscle, which was found to be involved Accordingly, the spermatic cord was isolated and the affected fascia was excised The dissection was then carried downward, necessitating the removal of a considerable portion of the fascia lata, and continued medially, requiring double ligation of the great saphenous vein, 2 cm and 5 cm below its entrance into the femoral vein Drainage was established through a stab wound in the lateral skin flap Pressure was maintained on the closed wound by a sea sponge dressing and snug binder



FIG 440 Lymphangioma of anterior abdominal wall The surgical specimen of the patient shown in Fig 439 It resembles a large sponge and consists of myriads of tiny saccules which contain lymph fluid (Pack and Ehrlich, Surg Gynec & Obst 79 177, 1944 *Courtesy*, Surgery, Gynecology and Obstetrics)

Convalescence was uneventful except for some necrosis of the skin flaps The resultant defect was satisfactorily covered with Thiersch grafts Follow-up examinations have revealed no recurrence of the tumor

The mass, which had been removed en bloc, had the appearance of a large, flat sponge. It was made up of locules containing straw-colored fluid (Fig 440) Microscopic examination of this tissue revealed the characteristic structure of lymphangioma.

CASE REPORT NO 81: GRANULATION TISSUE SARCOMA OF THE ABDOMINAL WALL

L. D., a 17 year-old white unmarried female was first seen at the Memorial Hospital on October 20 1943 for an abdominal tumor of 2 years duration One week prior to discovery of the mass the patient had sustained a moderately severe injury to the tumor site while sleigh riding A black-and blue mark appeared in the skin immediately following the trauma and the patient noted a swelling in this area 10 days later (probably a hematoma) This swelling did not increase perceptibly until she again injured the same portion of the abdominal wall one year later Following this second injury the mass slowly increased in size, but at no time was it painful

Physical examination revealed a smooth, fixed, hard, moderately tender mass measuring 5 cm in greatest diameter It was located just medial to the left anterior superior iliac spine The tumor was apparently situated intramurally was adherent to the crest of the ilium, and appeared to be inoperable because of its fixity

Aspiration biopsy did not yield tissue sufficiently characteristic to warrant an anatomic diagnosis.

On November 8 1943 an excisional biopsy was performed. A transverse incision was made over the lower portion of the mass and was carried down through the fascia of the external oblique muscle the internal oblique muscle, and the transversalis fascia all of which were split in the direction of their fibers. This exposed a soft unencapsulated hemorrhagic tumor from which a wedge of tissue was removed. There was no excessive bleeding The wound was closed in layers

Microscopic examination of this tissue revealed a vascular very cellular structure, *consisting for the most part of* large, ovoid cells with centrally placed prominent nuclei and granular cytoplasm Scattered areas of small spindle cells were also present. The blood vessels were numerous and thin-walled, and many contained hyalinized thrombi. The stroma was made up of a faint reticulin network. The general appearance suggested an angioblastic sarcoma on the one hand and an atypical granulosa-cell tumor on the other

Radiation therapy was given as follows 250 kv 1 5 mm of copper filter target–skin distance of 70 cm one port (10 × 13 cm) 300 r daily for a total dose of 3600 r This tumor proved to be extremely radiosensitive and regressed almost completely to palpation following completion of this treatment

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CHAPTER 28

Primary Retroperitoneal Tumors*

ANATOMIC, CLINICAL, AND PATHOLOGIC FEATURES

Pemberton and Whitlock credit Morgagni with the first description of a retroperitoneal tumor in 1761, said to be a retroperitoneal lipoma found at autopsy. Broca and Moynier subsequently reported the discovery of such tumors at autopsy. Lobstein is credited by Slagerman as being the first to apply the term *retroperitoneal tumors* to such lesions in 1829. In 1871 Howship Dickinson described a teratomalike tumor similar to the dermoid teratomas commonly found in the ovary. In 1889 Bassini described a retroperitoneal cystadenoma which resembled in structure a pseudomucinous cystadenoma of the ovary. In 1892 Vander Veer discussed the subject of retroperitoneal tumors before the American Surgical Association. At a meeting of the Southern Surgical Association in 1897 Douglas referred to a series of 20 cases of solid retroperitoneal tumors collected by Ragowski. As far as can be determined from a review of the literature, there have been approximately 750 cases of primary retroperitoneal tumors reported exclusive of this present series.

ANATOMY OF THE RETROPERITONEAL SPACE

The retroperitoneal space is partly actual and partly potential in concept. Broadly speaking, its uppermost margin is the diaphragm and its attachment to the body, while the pelvic diaphragm forms its caudal limit. It therefore extends from the twelfth dorsal vertebra and the twelfth rib above, down to the tip of the coccyx below. This space extends more laterally to the tip of the twelfth rib and a line dropped perpendicularly downward to a point on the iliac crest situated approximately at the junction of the anterior half with the posterior half of the crest. This line corresponds with the point at which the transversus abdominis muscle becomes aponeurotic by arising from the tips and borders of the transverse processes of the lumbar vertebrae.

Relations

The space is bounded anteriorly by the posterior layer of the parietal peritoneum, the posterior surface of the liver corresponding to its "bare area" portions

* In collaboration with Edward J Tabah.

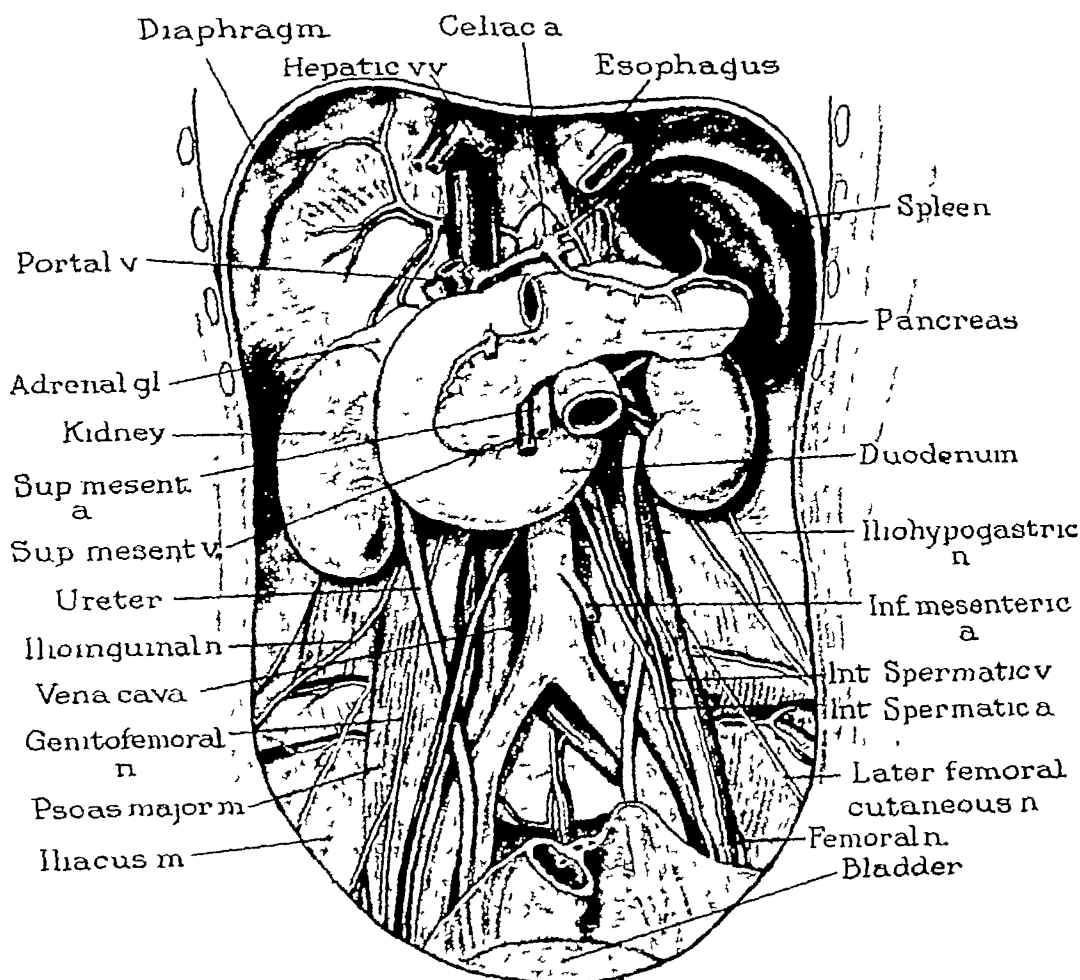


Fig 441 Anatomy of the retroperitoneal space, retroperitoneal viscera (Pack and Tabah, Surg Gynec & Obst 99 209, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)

of the ascending and descending colon and rectum, and a segment of the duodenum

The posterior wall of the space is bounded by the following muscles medially, the psoas muscle, lateral to it, the quadratus lumborum muscle, still further laterally, the tendinous portion of the transversus abdominis muscle These muscles have a definite fascial covering, which for the psoas is continuous below with the fascia covering the iliacus muscle The quadratus lumborum is covered by a fascial layer which is really the anterior layer of the lumbodorsal fascia These fascial layers are overlaid by a variable amount of fatty areolar tissue which fills the crevices between the muscles

In the iliac fossa the posterior wall is composed again of the continuation of the psoas major muscle medially, and laterally lies the iliacus muscle Below is the true pelvis, the posterior wall of which is composed of the following muscles (1) the obturator internus muscle extending over almost the entire inner surface of the side wall of the true pelvis below the line of the obturator nerve and covered by the very strong obturator fascia, (2) the piriformis muscle extending over the upper posterior wall of the pelvis and covered by a tenuous areolar fascia Inferiorly is the pelvic diaphragm, composed of the levator ani and the coccygeus, both of which are covered by a layer of pelvic fascia

The retroperitoneal space is further extended anteriorly to include those regions lying between the peritoneal leaves of the various intraabdominal mesenteries, namely, the mesentery of the small bowel, the transverse mesocolon, the mesosigmoid, and the mesenteries of the

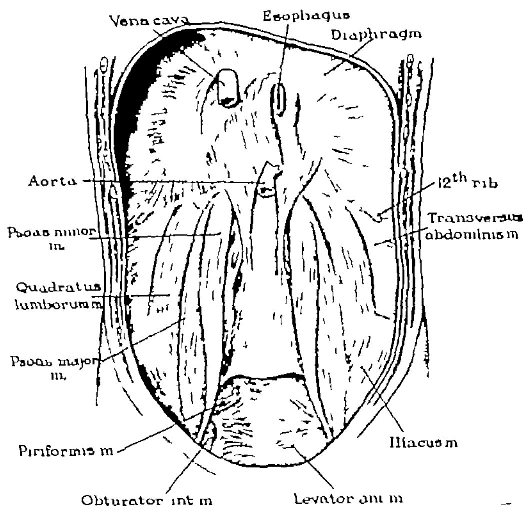


FIG 442. The retroperitoneal space; relation to posterior abdominal wall with viscera ablated. (Pack and Tabah, Surg Gynec. & Obst. 99 209 1954. *Courtesy* Surgery Gynecology and Obstetrics.)

ascending and descending colon when these are present. Tumors originating primarily within the mesenteric leaflets are quite infrequent, but some retroperitoneal neoplasms may invade the leaves of one or more of them and give the clinical impression of having arisen between them. We have also included for similar reasons those tumors which arise in the greater or lesser omentum

CONTENTS

Among the structures included in the retroperitoneal space are the abdominal aorta, the inferior vena cava, the portal vein, the pancreas the duodenum, the adrenal glands, and the kidneys and ureters. In addition to the major blood vessels their various large vascular branches are present such as the renal vessels, the splenic vessels, the celiac axis, the superior and inferior mesenteric vessels and the common, external, and internal iliac vessels and their branches The nervous tissue elements encountered here are the sympathetic trunks the celiac plexus the superior and inferior hypogastric plexus and their various extensions the anterior primary rami of D_{12} all the lumbar and sacral segments, the ilioinguinal the iliohypogastric, the lateral cutaneous nerve of the thigh the genitofemoral the femoral, obturator the sciatic, the pudendal, and the various nerves and branches of the sacral plexus Filling the various crevices in and around the above structures is a loose cushion of fatty and areolar tissue

Finally two other structures are of importance the embryologic remnants of the primitive urogenital cell ridge, which

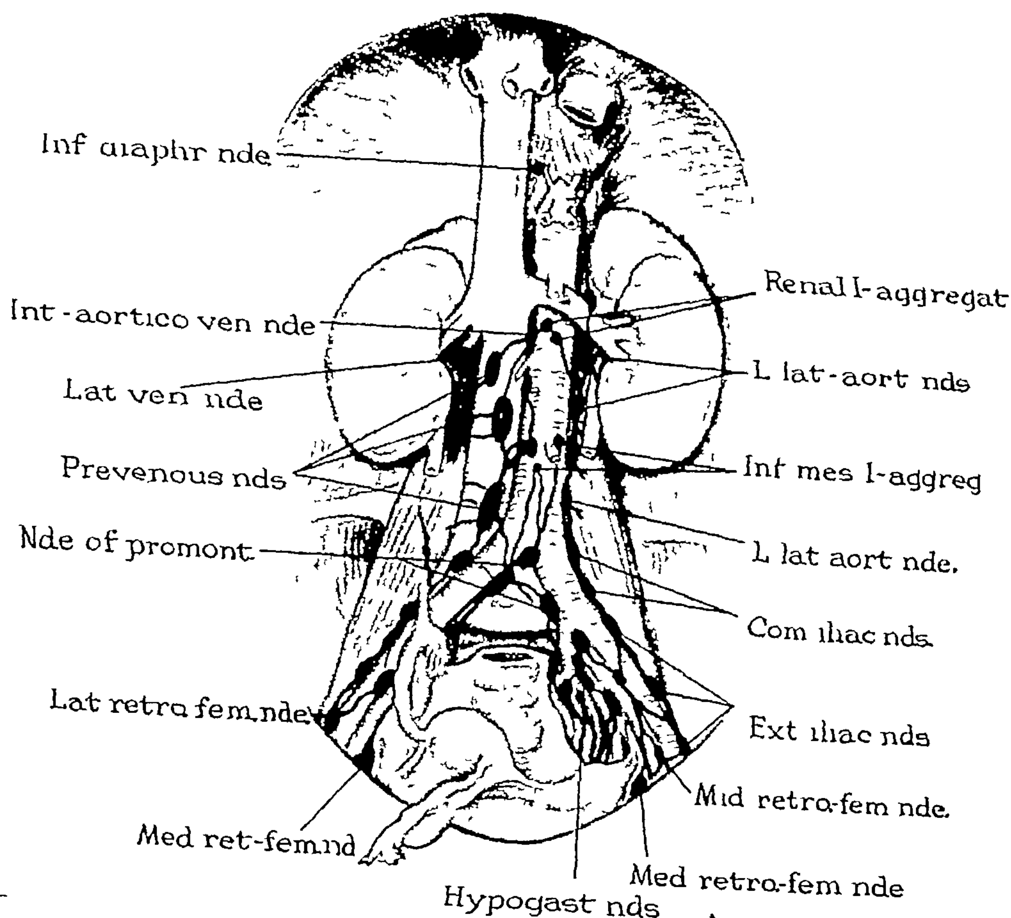


FIG 443 Lymphatic anatomy of the retroperitoneal space, the paravascular lymph-node distribution (Pack and Tabah, Surg Gynec & Obst 99 209, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)

will be considered in further detail in the discussion of the origin and histogenesis of retroperitoneal tumors, and the lymphatic vessels and lymph nodes

LYMPHATIC ANATOMY

LYMPH NODES

The lymph nodes are distributed in two great groups the visceral and parietal aggregates The visceral lymph nodes lie in relation to the superior and inferior mesenteric arteries and to the branches of the celiac axis, and consist of (1) the hepatic group, which is distributed along the hepatic artery or its branches, (2) the gastric group, which lies on the left gastric artery, and (3) the pancreaticolienal group, which extends along the splenic artery and its branches The parietal lymph nodes are arranged in the following groups (1) external iliac, (2) internal iliac, (3) common iliac, (4) sacral, (5) lumbar or aortic nodes, and (6) inferior diaphragmatic nodes

The *external iliac nodes* form three chains· (1) The lateral chain, composed of two to four nodes placed along the lateral border of the external iliac artery. The lowermost node which lies in relation to the origins of the inferior epigastric and the deep circumflex iliac arteries is the largest and most constant of this group (2) The middle, or intermediate, chain consists of two or three nodes placed on the medial side of the artery and on the anteromedial surface of the external iliac vein The node situated at the angle of separation of the external iliac and hypogastric arteries is the most constant (3) The medial chain consists of two to four nodes which lie internal to the vessels The lowermost node of this chain lies behind the medial

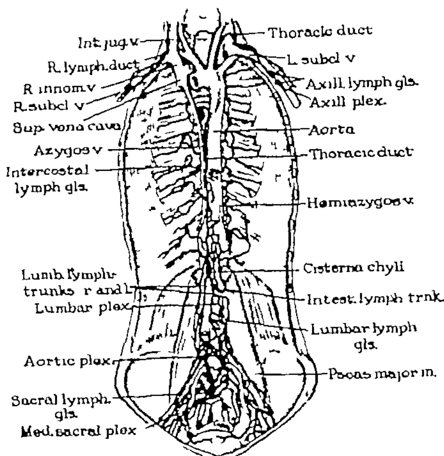


FIG. 444 Lymphatic anatomy of the retroperitoneal space the lymphatic collecting trunks. (*Pack and Tabah, Surg Gynec. & Obst.* 99:209 1954 *Courtesy* Surgery Gynecology and Obstetrics.)

compartment of the femoral sheath and is a continuation of the deep inguinal or the node of Cloquet. The lymph drainage from the external iliac nodes is upward to the common iliac nodes

The *hypogastric or internal iliac nodes* number from four to eight and are placed opposite or in the angles formed by the branches of the hypogastric artery as they deviate from each other near the parent trunk. The efferent lymphatics from the hypogastric nodes pass to the common iliac nodes.

The *common iliac nodes* are arranged in three sets the lateral, medial, and middle groups (1) The lateral group consists of two or three nodes situated along the lateral border of the common iliac artery and lying on the psoas muscle representing a continuation of the external iliac nodes (2) The medial group consists of two to four nodes and occupies the angle formed by the deviation of both common iliac arteries These nodes lie on the left common iliac vein and lower down on the lower portion of L_5 vertebra and the disc between L_5 and the sacrum. (3) The middle, or retrovascular group lies behind the common iliac blood vessels It consists of one to four nodes that lie anterior to the obturator nerve and the lumbosacral nerve trunk. The lymph from the common iliac nodes passes to the lumbar or aortic nodes

The *sacral nodes* consist of two or three nodes placed along the lateral sacral arteries opposite the second and third sacral foramina, in the hollow of the sacrum. They drain to the lumbar or aortic nodes

The *aortic nodes* consist of approximately 40 to 50 nodes around the aorta and the inferior vena cava and are di

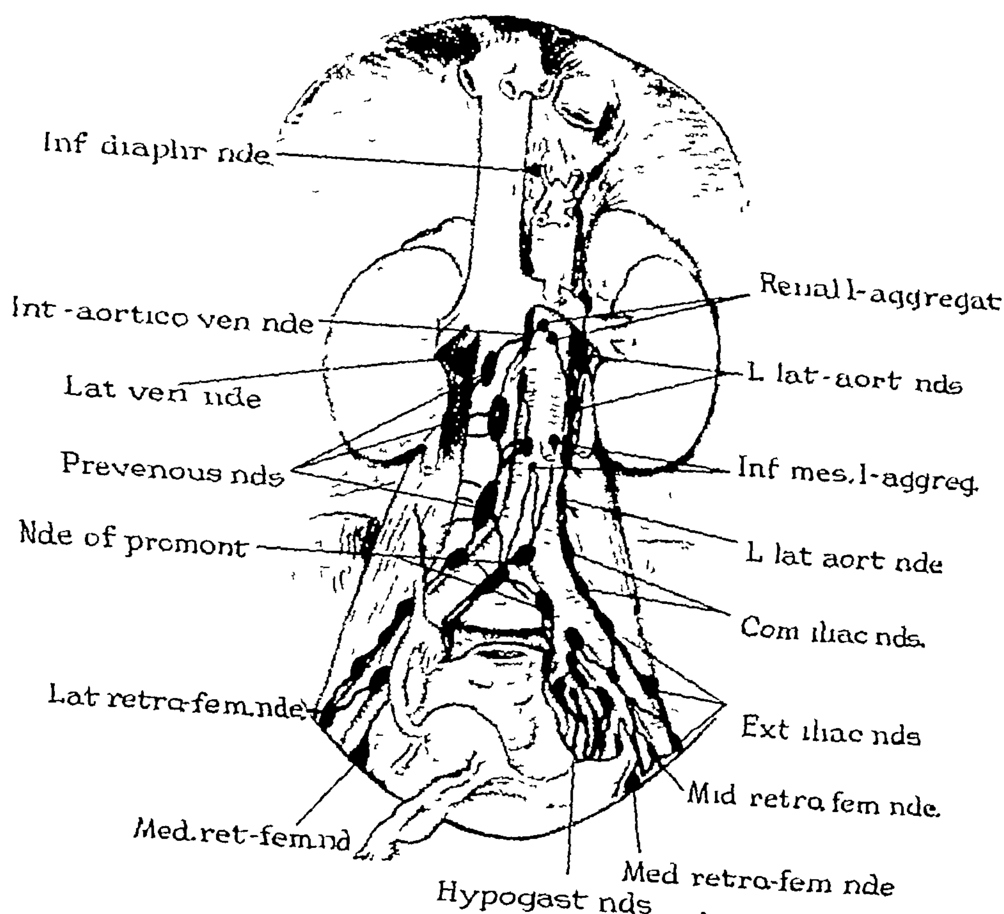


Fig 443 Lymphatic anatomy of the retroperitoneal space, the paravascular lymph-node distribution (*Pack and Tabah, Surg Gynec & Obst 99 209, 1954 Courtesy,* Surgery, Gynecology and Obstetrics)

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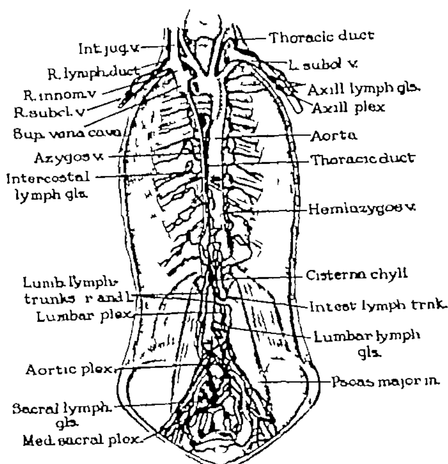


Fig. 444. Lymphatic anatomy of the retroperitoneal space: the lymphatic collecting trunks. (Pack and Tabah, Surg. Gynec. & Obst. 99:209, 1954. Courtesy Surgery, Gynecology and Obstetrics.)

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vided into four main groups (1) The preaortic nodes are divided into four main groups, each group lying on the aorta in relation to the main stem of the blood vessel of the same name, *viz*, the celiac, the superior mesenteric, the renal, and the inferior mesenteric Each consists of two to four nodes The renal nodes are placed in front of the aorta along the lower border of the left renal vein (2) The right paraaortic nodes are placed on the right side of the abdominal aorta in three main positions (a) between the aorta and the inferior vena cava, (b) on the right side of the inferior vena cava, and (c) behind the inferior vena cava (3) The left paraaortic nodes consist of a chain of five to ten nodes placed along the left side of the abdominal aorta (4) The retroaortic nodes are relatively small and unimportant

Finally there are the *inferior diaphragmatic nodes* consisting of one to three nodes placed against the inferior surface of the diaphragm, usually near the origin of the inferior phrenic arteries and their branches

MAJOR LYMPH TRUNKS

The efferent lymphatics of the paraaortic nodes unite to form a single trunk on each side, the right and left lumbar lymph trunks, which unite to form the cisterna chyli The cisterna chyli lies in front of the bodies of the first and second lumbar vertebrae between the aorta and the right crus of the diaphragm and receives, in addition to the above, the intestinal trunk which passes from the preaortic nodes Leaving the cisterna is the thoracic duct which leaves the abdomen through the aortic orifice of the diaphragm

HISTOGENESIS OF RETROPERITONEAL TUMORS

Tumors in the retroperitoneum may arise from fat, areolar connective tissues, fascia, muscle, vascular tissue, somatic and sympathetic nervous tissue, and lymphatic vessels and nodes There are other neoplasms of less frequency, such as the smooth-muscle tumors, complex teratomas, embryonal carcinomas, embryonal rhabdomyosarcomas, and certain bizarre cysts of unknown origin

A brief review of the embryology of the urogenital apparatus demonstrates the possible origin of some of these neoplasms In the human embryo there appear during development three distinct excretory organs of which the most primitive is the pronephros, a rudimentary structure of transitory appearance The pronephric duct is formed by a caudad extension of the distal end of each pronephric tubule, meeting and fusing with the tubule behind to form a continuous channel which eventually opens into the cloaca The duct persists and participates in the formation of the mesonephros, which is derived from the intermediate mesoderm, or the nephrogenic cord As the mesonephric tubules (approximately 38 in number, according to Felix) grow out, they soon open into the pronephric duct, which is now called the *mesonephric duct* or *wolffian duct* Degeneration of the mesonephric tubules begins before the caudal extension is complete, but it is reasonable to suppose that sometimes one or more of these may remain as a vestigial structure and later give rise to a retroperitoneal tumor

The metanephros arises from the caudal quarter of the neophrogenic cord to form the glomeruli and secretory tubules of the adult kidney

The wolffian duct is the primary excretory duct of the pronephros and mesonephros and terminates in the cloaca It gives rise to the ureteric bud just before it enters the cloaca and in the male is represented by the ducts of the epididymis and the vas deferens, and in the

female by Gartner s duct. The müllerian duct develops medial to the wolffian duct from an invagination of the celomic mesothelium into the summit of the urogenital fold in the region of the second and third thoracic segments. The mullerian duct disappears in the male except for the hyatids of Morgagni and the sinus pocularis (male uterus) whereas in the female it does not degenerate but forms the fimbria, fallopian tubes, uterus and vagina. The urogenital fold shortly after its formation divides into a lateral mesonephric ridge and a medial genital ridge, the mesothelium of which is continuous There is a difference of opinion as to whether the definitive germ cells arise from overlying mesothelial cells and later invade the genital ridge, or whether they arise from the yolk-sac entoderm or some other focus and migrate from their site of origin down into the genital ridge.

The concept that retroperitoneal tumors arise from remnants of the urogenital apparatus originated with Roth, who was the first to correlate the relationship between retroperitoneal cystic tumors and wolffian body remnants Later in 1900 Dowd asserted that the cellular rests of the wolffian body pushed their way between the leaves of the mesentery to give rise to cysts Handfield Jones in 1924 supported the view that cysts of the retroperitoneum in all probability arose from remnants of various elements of the urogenital apparatus More recently Hansmann and Budd found from a study of 17 personally observed cases that tumors developing in the retroperitoneal space were similar to neoplasms having their origins in adult urogenital organs and suggested, therefore, that the precursors of such tumors were the embryonic urogenital remnants They postulated that smooth-muscle neoplasms found in the retroperitoneal space and without organ attachment came from embryonic müllerian tissue. Mixed mesodermal tumors containing fat, fibrous tissue, angiomatous tissue, glandular tissue, etc. were also explained as arising from embryonic urogenital tissue which is capable of giving rise to tissues of divers types

SYMPTOMATOLOGY AND DIAGNOSIS

SYMPTOMATOLOGY

Early symptoms are characteristically lacking because retroperitoneal tumors grow in the loose areolar tissue and may reach a large size before symptoms herald their presence.

The most frequent initial complaint of the patients in our series was abdominal pain (50 8 per cent) Such pain was rarely severe or incapacitating. Next in frequency of complaints was the discovery by the patient of a definite abdominal mass or his awareness that the abdomen was becoming progressively larger (30.8 per cent) The swelling was rarely associated with pain (in only 5 per cent of the cases were the two associated as initial symptoms) but in later stages abdominal pain did occur more

TABLE 97 INITIAL COMPLAINTS OF PATIENTS WITH RETROPERITONEAL TUMORS

Initial Symptoms	*Number of Patients*	*Frequency of Symptoms*
Number of patients	120	
Abdominal pain	61	50 8
Abdominal mass or swelling	37	30 8
Gastrointestinal symptoms	24	20 0
Backache	8	6 7
Pain down leg and/or swelling of leg	8	6 7
Genitourinary symptoms	3	2 5
Weight loss	3	2 5
Heaviness in perineum	2	1 7
Fever	1	0 8

TABLE 98 INCIDENCE OF HISTOLOGIC TYPES OF RETROPERITONEAL TUMORS (Authors' Series)

A. MALIGNANT TUMORS				
Total cases		103		
Rhabdomyosarcoma			Fibrosarcoma	6
Adult	15		Neuroblastoma (extraadrenal)	1
Embryonal	7		Ganglioneuroma	1
Liposarcoma		17	Mesothelioma	2
Lymphoma			Myxoma	2
Lymphosarcoma	18		Malignant schwannoma	1
Hodgkin's disease	6		Hemangiopericytoma	1
Leiomyosarcoma		5	Synovioma (synovial sarcoma)	1
Sarcoma of undetermined histogenesis		8	Chordoma	1
Carcinoma			Pheochromocytoma (extraadrenal)	1
Anaplastic (no known primary site)	6			
Embryonal	1			
B BENIGN TUMORS				
Total cases		17		
Cyst		5	Lipoma	2
Xanthogranuloma		3	Neurilemmoma	1
Leiomyoma		2	Complex teratoma	1
Fibroma		2	Pheochromocytoma (extraadrenal)	1

frequently (Table 99) The frequency of the other initial symptoms is listed in Table 97

AGE AND SEX

The majority of patients with retroperitoneal tumors were in the fifth and sixth decades of life In Donnelly's series of 95 cases, 58 per cent of the patients were over the age of 40, in our group 61 7 per cent were over 40 More than 14 per cent of the tumors occurred in patients under the age of 10 years The high incidence in children was emphasized by Donnelly and more recently by Newman and Pinck, who found a 15 per cent incidence under 10 years The significance of this figure becomes more impressive when one considers that the most frequent tumors of infancy and childhood—Wilms's tumor of the kidney and neuroblastoma arising in the adrenal gland—were not included in this survey The average age of the patients was 41 3 years The sex incidence in our series favored the females by only 6 6 per cent, which is not statistically significant Donnelly found the ratio of frequency to favor males 1 5 to 1

DIFFERENTIAL DIAGNOSIS

After a lesion has been diagnosed as a retroperitoneal mass, it is frequently impossible to determine its specific nature until the operation and occasionally then only by histologic examination of the excised or biopsied specimen A presumptive clinical diagnosis can be tentatively held by a consideration of such factors as the age and sex of the patient, the location of the tumor and evidences of its functional activity, together with the obvious physical signs and radiologic findings In younger patients the principal lesions to be considered are Wilms's tumor of the kidney, neuroblastoma o ganglioneuroma, teratoma, embryo sarcoma, adrenocortical tumor, and a dominal lymphoma The Wilms's emb onal adenomyosarcoma is usually acc rately determined by intravenous or ret rograde pyelograms Teeth or other ev dence of calcification in a roentg gram would suggest a terato

though calcification occurs also in neuroblastomas Neoplasms of the adrenal gland are generally accompanied by endocrine changes, but when these are lacking the diagnosis becomes more difficult. To determine the specific nature of the lesion preoperatively in an adult is always a much more challenging problem.

PHYSICAL DIAGNOSIS

An abdominal tumor or mass was found on the initial physical examination elsewhere or at Memorial Hospital in almost every case Tenderness of the abdominal mass was specifically recorded in only 25 patients or 20 8 per cent. The *majority of these tumors therefore were* not tender In 21 instances a palpably enlarged liver was ostensibly due to metastases Ascites due to compression of the portal vein was present in 15 patients in 3 additional patients the ascites

TABLE 99 LATER SYMPTOMS OF PATIENTS WITH RETROPERITONEAL TUMORS AT TIME OF ESTABLISHMENT OF THE DIAGNOSIS

Later Symptoms	*Number of Patients*	*Frequency of Symptoms*
Number of patients	120	
Abdominal mass or swelling	44	36 7
Weight loss	41	34 2
Gastrointestinal symptoms	33	27 5
Abdominal pain	17	14 2
Pain and/or swelling of leg	13	10 8
Fever	10	8 3
Weakness and asthenia	8	6 7
Genitourinary symptoms	7	5 8
Respiratory symptoms	5	4 2
Back pain symptoms	3	2 5

was probably due to peritoneal metastases *Hematemesis* was recorded in 6 patients, but it was never determined whether or not this was due to esophageal varices secondary to portal obstruction. In children fever anemia, and dilated superficial abdominal veins were regularly noted. Scrotal varicoceles are ipsilateral to the location of the retroperitoneal tumor

RADIOGRAPHY

Newman and Pinck stated that in 53 per cent of their patients roentgen ray findings in the gastrointestinal tract and

TABLE 100 AGE AND SEX OF PATIENTS WITH RETROPERITONEAL TUMORS

Age	*Number*	*Per Cent*	*Male*	*Female*
Total cases	120	100 0	56	64
1 year and less	2		1	1
2–5 years	11	14 1	8	3
6–9 years	4		3	1
10–19 years	4		1	3
20–29 years	12	24 2	2	10
30–39 years	13		7	6
40–49 years	25		8	17
50–59 years	24	61 7	14	10
60–69 years	18		9	9
70–79 years	7		3	4

retrograde pyelography were sufficient to establish a diagnosis Such radiographic studies serve a double purpose by excluding the possibility of a primary tumor originating in the gastrointestinal or genitourinary tract and by pointing the diagnostic finger of suspicion to a retroperitoneal mass because *of changes in contour or position in one* or more of these organs Morton recently presented a valuable and comprehensive discussion on the subject of organ displacement by abdominal tumors of different types and in various locations Additional roentgenologic aids include an ordinary flat plate of the abdomen pneumoperitoneum, perirenal insufflation of air and abdominal aortography and venography

The retrograde or intravenous pyelogram is the most valuable of all radiologic technics in demonstrating the presence of a retroperitoneal tumor by pressure, distortion or displacement of the kidneys ureters, or bladder Films taken not only in the anteroposterior but also

in the lateral and even the oblique projection are essential The anteroposterior view, for example, will enable one to detect lateral or medial deflections of the ureters, whereas lateral films may demonstrate anterior displacement Partial or complete obstruction of the ureter resulting in varying degrees of hydroureter and hydronephrosis is another significant finding Tumors pressing on the kidney may distort calyces and pelvis, and permit the detection of abnormal rotation and displacement of the kidney from its normal position Emmett and Schulte found renal and ureteral displacement in 72 5 per cent of the cases of retroperitoneal tumors which they studied Retroperitoneal tumors within the pelvis may cause compression or displacement of the bladder to a more anterior position

The distortions of the gastrointestinal tract, as visualized by gastrointestinal x-ray series and barium enema, are important The films should be taken in many planes in order to detect displacement For instance, the stomach may be displaced medially, laterally, anteriorly, downward, or upward, similarly, the duodenum and small bowel may be shifted in position, and the ascending, descending, or sigmoid colon may be pushed anteriorly alone or else anteriorly and medially or laterally Pelvic tumors may push the rectum anteriorly, laterally, or in both directions

Sheinmel and Mednick found that the left-lateral-upright projection in the gastrointestinal x-ray series was helpful in demonstrating lesions of the left upper abdominal quadrant and the corresponding retrogastric space It was of limited value for midline epigastric tumors and of no value for those in the right paravertebral area. The right-lateral-upright projection was of no value in demonstrating possible masses in any of the above-mentioned regions because the major portion of the stomach was to the left of the midline, and this resulted in a large projectional distortion factor With the patient in the right-lateral-recumbent position mobility of the cardia and upper pars media of the stomach was demonstrated, and there was a shift of that portion of the stomach to the right The antral position, being fixed, showed little or no shift With the patient in the left-lateral-recumbent position there was a definite shift of the cardiac portion of the stomach to the left and much less shift of the pars media. This mobility of the gastric segments was employed to visualize masses high in the epigastric, midepigastric, and paravertebral regions

Roentgenograms of the chest may show elevation of the diaphragm, particularly with large upper abdominal tumors The films also serve to rule out lung metastases

In our series of cases significant findings to indicate a suspicion of an extrinsic lesion, if not a definite retroperitoneal tumor, were present in 63 out of 104 cases which had recorded either one or more of the following preoperative procedures retrograde or intravenous pyelograms, gastrointestinal series, or barium enema This is an incidence of 60 5 per cent positive diagnosis utilizing the above radiologic means alone. It is apparent that if combined with other diagnostic procedures, such as the history and physical examination, the percentage of correct preoperative diagnoses should be somewhat greater

Perirenal Aerograms

These have been utilized by Cahill and others in the detection of tumors of the adrenal glands and kidneys Retroperitoneal tumors in relation to these organs have also been diagnosed with this technic The procedure, however, is not without danger from air embolism and its use should be restricted only as the final diagnostic effort

Pneumoperitoneum was tried in several of our cases but failed to yield sig-



FIG 445. Retroperitoneal pneumograms. (*Left*) The retroperitoneal air outlines a tumor of the superior pole of the left kidney Concurrent pyelogram (*Right*) The retroperitoneal air reveals a tumor (lipoma) suprajacent to a normal left kidney (Pack and Tabah, Surg. Gynec. & Obst. 99 209 1954. *Courtesy* Surgery Gynecology and Obstetrics.)

nificant or characteristic findings It may be more successful in intraperitoneal tu mor masses Carbon dioxide gas (Alvar ez) is more rapidly absorbed than air so may be used to shorten the discomfort.

PNEUMORETROPERITONEUM

Ruiz Rivas in 1948 injected oxygen through a single puncture into the pre-coccygeal areolar tissue. Through this readily accessible puncture point the gas diffuses upward through the deep areolar tissues producing a subserous em physema, resulting in a pneumopara metrium, pneumoretroperitoneum, and even a pneumomediastinum. The hazard of air embolism is slight and it is su perior to pneumoperitoneum and peri renal insufflation in demonstrating space-occupying masses in or against the abdominal viscera.

ABDOMINAL AORTOGRAMS

The technic for direct translumbar aortography was reported in 1929 by dos Santos A long, preferably malleable needle is inserted 2 cm. below the 12th rib margin and 7 cm. to the left of the midline. The needle is angled medially anteriorly and somewhat cephalad. The anterolateral aspect of the vertebral body serves as a landmark and the aorta generally lies about 2 cm. deep to this point. One may either employ a 30 to 70 per cent solution of sodium iodide, or use an organic iodide such as iodoxyl (Neo-Iopax) and iodopyracet (Diodrast) as the contrast medium The or ganic iodides have a greater margin of safety and fewer reactions than sodium iodide If the abdominal aorta and its main branches are to be visualized, the film is exposed immediately following the injection When information regard ing the iliac vessels is desired, a delay of several seconds is necessary Abdominal arteriography is a valuable adjunct in the diagnosis of retroperitoneal tumors This method of investigation is particu larly valuable in ruling out lesions of the kidney and adrenal such as neoplasms cysts, and hydronephrosis, as

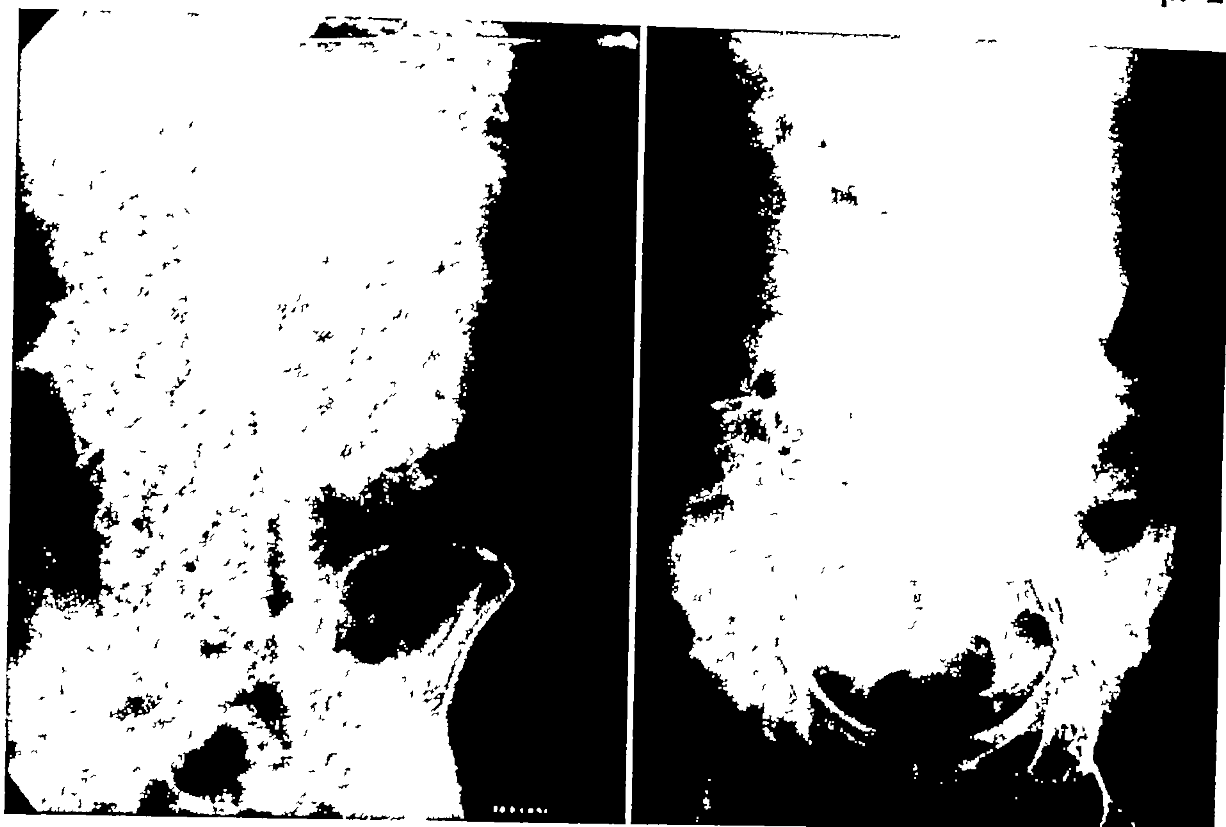


FIG 446 Aortograms in a patient with a retroperitoneal rhabdomyosarcoma The tumor obstructed the abdominal aorta (*Left*) Translumbar aortogram revealing obstruction of the aorta and great distention of arterial radicles (*Right*) Retrograde aortogram in same patient using a femoral-artery polyethylene catheter (Pack and Tabah, Surg Gynec & Obst 99 209, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)

well as aneurysm of the abdominal aorta The size and position of the tumor are usually much better defined than on the plain roentgenogram The tumor may be so large as to displace the aorta itself or some of its major branches One can usually gain information as to the vascularity of the tumor Wagner *et al* state that pooling of radiopaque material, which can occur in areas of hemorrhage and necrosis within the tumor, is highly suggestive of malignancy

ABDOMINAL VENOGRAPHY

The use of abdominal venography can prove extremely useful, particularly in those cases where the tumor compresses and displaces or obstructs the inferior vena cava and/or the common iliac veins The site of compression and displacement and the established collateral circulation can be studied The technic reported by Farinas utilizes the long saphenous vein for injection of the opaque medium under direct vision

INCIDENCE AND TYPES OF RETROPERITONEAL TUMORS

Of the total 120 cases, 103, or 85 8 per cent, were diagnosed as malignant (see Table 98) Donnelly found 91 per cent of his group of primary retroperitoneal tumors to be malignant. There was a total of eight of undetermined histogenesis There were, in addition, six cases which could only be classified as anaplastic or undifferentiated carcinoma and presumed to be primary in that region There were no other proved sources of tumor in spite of extensive investigation, operative exploration, and in several instances postmortem examination This group, together with the undifferentiated sarcomas, formed a total

of 14 cases or 11.7 per cent. Donnelly found 23 cases of undifferentiated neoplasm an incidence of 24.2 per cent, and Newman and Pinck had six such cases, or 18 1 per cent.

Among the malignant tumors there were 22 cases of rhabdomyosarcoma, 7 of which occurred in infants and young children lymphosarcoma occurred in 18 patients (16 typical round-cell lymphosarcoma and two giant follicular sarcoma) Hodgkin s disease in 6 liposarcoma in 17 and other types of sarcoma were responsible for another 11 cases This group of diagnosed sarcomas accounted for the majority of the malignant tumors 77 cases or 74.8 per cent. Among other interesting neoplasms was a malignant schwannoma, a chordoma which appeared as a huge lower abdominal mass a malignant synovioma, which, as far as we are aware from a review of the literature, has never previously been recorded in this region There were two cases of mesothelioma Two unusual tumors were a hemangiopericytoma and an extraadrenal pheochromocytoma, both classified as malignant.

The most frequent benign tumors were the epithelial cysts (five cases) Next in frequency were three cases of xanthogranuloma, which was originally described by Oberling as occurring in the retroperitoneum There were two examples of each of the following lipoma, leiomyoma, and fibroma. There was one neurilemmoma, one benign extra adrenal pheochromocytoma, and one teratoma. Taking all tumors in our group both benign and malignant it is readily apparent that tumors of mesodermal origin form by far the most frequent group (68.3 per cent) occurring in the retroperitoneum

RETROPERITONEAL CYSTIC AND TERATOMATOUS TUMORS

Retroperitoneal cysts are rare. Handfield Jones defines them as "those cysts lying in the retroperitoneal fatty tissues which have no connection with any adult anatomic structure save by areolar tissue." Although there is still no unanimity as to the nature and origin of these cysts, the most popular view is that they arise from persistent remnants of the early urogenital system.

The following classification is a modification of the one given by Handfield Jones (1) cysts of urogenital origin, (2) cysts of mesocolic origin (3) teratomatous and dermoid cysts (4) lymphatic or chylous cysts.

CYSTS OF UROGENITAL ORIGIN

According to Handfield Jones the majority of these cysts occur near the kidney or behind the colon, and near the head or tail of the pancreas They are found in patients between the ages of 15 and 50· Handfield Jones asserts that they occur more frequently on the left side of the abdomen than the right. They are said to be of much greater frequency in the female sex.

One definite criterion which denotes that the cyst is of urogenital origin is the rare finding of primitive glomeruli or renal tubules in the cyst wall. These cysts have a thin smooth fibrous wall with an epithelial lining The contents may be clear fluid or chocolate-colored from an admixture of blood. The epithelium lining the cyst is usually of low columnar type, or rarely may be flattened.

The signs and symptoms are essentially the mechanical effects of pressure by the tumor on adjacent structures Obstruction of the lacteals by a large mesenteric cyst is not unusual on opening the peritoneal cavity the markedly dilated lacteals may be an impressive sight.

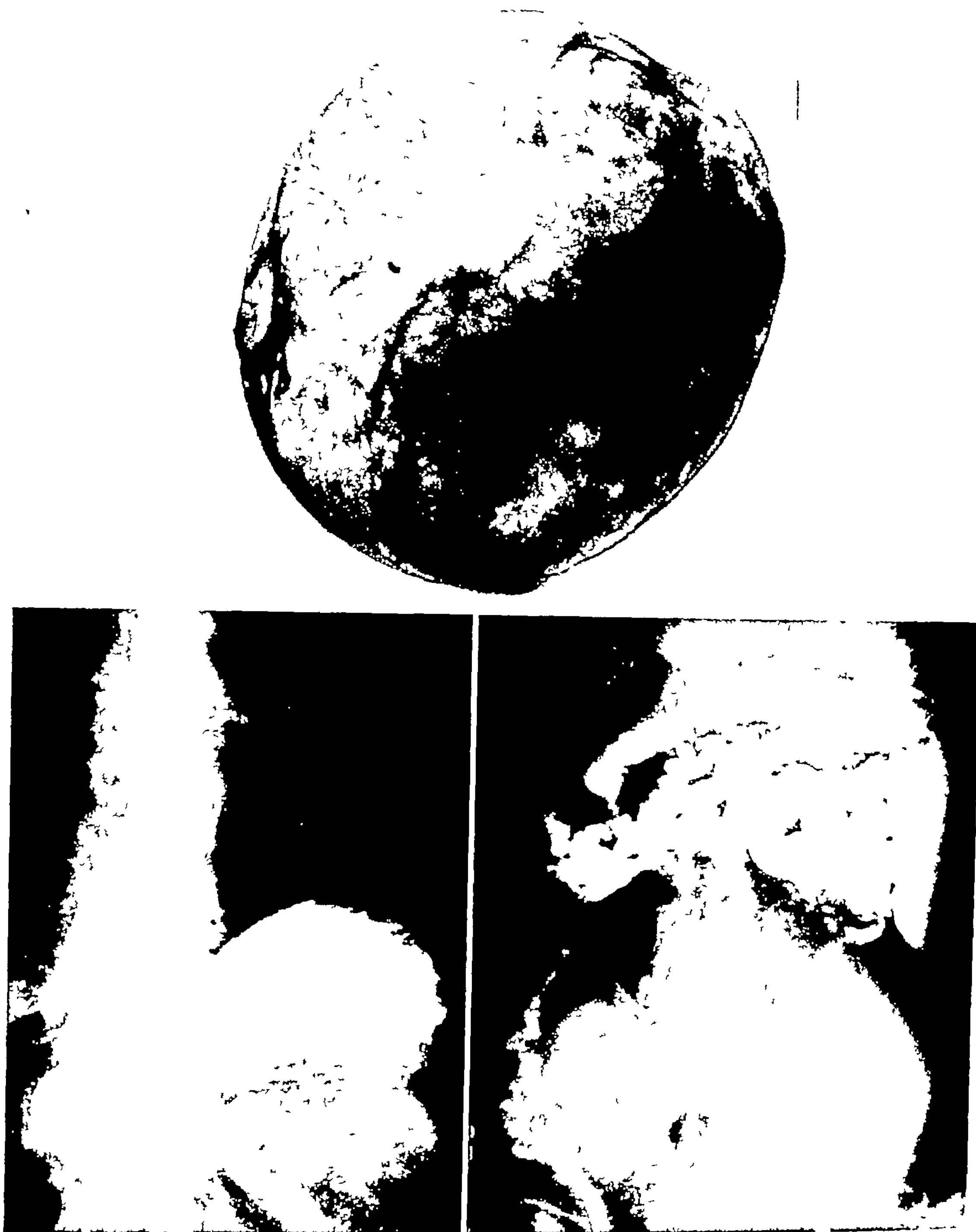


FIG 447 Retroperitoneal cysts (*Upper*) Simple cyst Surgical specimen (*Lower left*) Showing extrinsic pressure on stomach by retroperitoneal cyst (*Lower right*) Huge retroperitoneal cyst in lower abdomen displacing small intestines (Pack and Tabah, Surg Gynec & Obst 99 209, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)

PROGNOSIS AND TREATMENT

These cysts are usually benign and the prognosis is good Maury, Hinman, and others state that they occasionally become malignant and metastasize, but we have never observed this complication

The only treatment of retroperitoneal cysts is complete surgical excision Although these cysts are usually adjacent or adherent to nearby organs, as a rule they shell out or enucleate quite readily Occasionally, in the case of extremely large cysts or in otherwise complicated cases, or in poor-risk patients, one may need to marsupialize the cyst and carry out a multiple-stage procedure It is frequently necessary to resect a segment of adjacent intestines, because in totally ex-

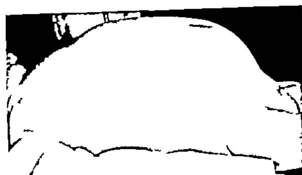


Fig. 448. Retroperitoneal teratoma in an infant. (Pack and Tabah, Surg Gynec. & Obst. 99:209 1954. *Courtesy* Surgery Gynecology and Obstetrics.)

tirpating the cyst the blood supply to the adjacent bowel may be seriously im paired.

CYSTS OF MESOCOLIC ORIGIN

These cysts, although very similar to the urogenital cysts, arise in a different manner They are found in the region between the ascending and descending colon and below the transverse mesocolon, and are said to arise from imperfect fusion of the layers of the peritoneum They are composed of a fibrous wall lined by a low columnar epithelium Handfield Jones distinguishes these cysts from the true urogenital cysts by their location, they lie anterior to the sper matic or ovarian vessels whereas the lat ter lie posterior to them.

TERATOMAS AND DERMOID CYSTS

The teratomas are congenital tumors composed of multiple tissues dissimilar to the viscera or tissues of their origin. Dermoid cysts are highly differentiated teratomas consisting of mature adult tissues The simplest dermoid cyst, if properly and completely examined, may con tain structures derived from all three germ layers. A highly malignant teratoma composed of only one type of un differentiated embryonic tissue may oc casionally be encountered. The degree of differentiation of the tissues in a tera toma is of practical value since the ma



Fig. 449 Features of gross specimen of ret roperitoneal teratoma in an infant shown in Fig. 448. (Pack and Tabah, Surg Gynec. & Obst. 99:209 1954. *Courtesy* Surgery Gynecology and Obstetrics.)

lignancy tends to vary inversely with the differentiation. Most teratomas contain a mixture of both cystic and solid tissues, the latter consisting of mixtures of ma ture and embryonic tissues Because of their tendency to be partially cystic we have included this tumor with cysts in general.

After the ovaries and testes, the retroperitoneal and sacrococcygeal region is the most frequent site of teratomas Of a total of 82 cases of teratoma studied by Willis, 50 (61 per cent) were found in the ovary 19 (23 per cent) in the testis, and 5 (6 per cent) in the retroperitoneal and sacrococcygeal regions

Incidence, Sex, and Age

Palumbo *et al.* in 1949 reviewed the subject of primary teratoma of the later al retroperitoneal spaces and stated that up to 1948 there was a total of 58 proved cases reported in the literature. Palumbo estimates that approximately 11 per cent of primary retroperitoneal tumors are teratomas In the series of retroperitoneal tumors reported by Frank, 9.3 per cent were teratomas Of 29 cases of presumably primary retroperitoneal teratoid

tumors submitted to the Armed Forces Institute of Pathology between 1942 and 1947, 23 cases were found by Friedman to have identical lesions in one or other of their testes

The sex appears to be in favor of females Palumbo estimates 57 per cent female These tumors are more commonly found in young children and infants In his review Palumbo found that 30 per cent of the patients were in the first year of life, 55 per cent in the first decade, 10 per cent in the second decade, 25 per cent in the third decade, and only 10 per cent were over the age of 30 years The average age of patients was 13 years

Malignancy

Palumbo *et al* state that of 58 retroperitoneal teratomas reviewed, six (10 per cent) were malignant Metastases to the lungs, liver, lymph nodes, and brain occur.

Diagnosis, Treatment, and Prognosis

Just as in other retroperitoneal tumors, the most common complaint is abdominal enlargement, a palpable mass, or abdominal or back pain

The specific diagnosis is rarely made preoperatively unless one sees evidence in the x-ray film of teeth, bone, or other calcified deposits The age of the patient will be of some assistance in arriving at a diagnosis, otherwise one must be content with making a diagnosis of retroperitoneal tumor by the methods previously discussed According to Arnheim, half of the retroperitoneal teratomas in the literature were described at autopsy

Palumbo states that of 39 cases operated on and followed, the patient mortality was 54 per cent The over-all mortality of the group was 70 per cent Arnheim's extensive review of the literature in 1943 revealed that of the 23 cases recorded there were 11 operated on with 8 deaths, or 72 5 per cent mortality The remaining 12 untreated patients all died. The operative deaths were ascribed to incomplete removal, hemorrhage, and shock.

The only treatment is prompt removal of the tumor

LYMPHATIC OR CHYLOUS CYSTS

Lymphatic or chylous cysts may occur retroperitoneally or within the mesentery They may arise on a mechanical or obstructive basis, or they may be due to some developmental defect and are then said to be similar to the mediastinal and cervical cystic lympangiomas They are quite rare, and according to Newman and Pinck only 8 cases were reported up to 1950 Moynihan mentions that dilatation of the cisterna chyli may be the cause They may be difficult to differentiate from cysts of urogenital origin The fluid content, however, of a lymphatic cyst is usually thick, creamy white or yellow and according to Moynihan has a specific gravity of between 1012 and 1020, and has microscopic evidence of fat globules and finely granular amorphous-like material No such lesions were encountered by us

ENTEROGENOUS CYSTS

Enterogenous cysts may arise in one of the following manners

1 Cysts of intestinal origin (a) In the 20–30 mm embryo true diverticula may be found projecting from the antimesenteric border of the intestinal tract They normally disappear, leaving no trace of their existence Occasionally, however, they continue to grow and become closed off from the intestinal lumen to form a cyst This type of cyst is generally found between the various layers of the bowel wall Its occurrence does not concern us in this discussion

(b) According to Bremer in the 10-mm. embryo the intestinal tract consists of a solid mass of proliferating epithelial cells These cells later secrete a fluid which gathers between the cells and forms vacuoles By a coalescence of these vacuoles a lumen is ultimately formed. However there are many opportunities for abnormal canalization during this procedure For example, a chain of vac uoles may coalesce only with each other and not with the main lumen This will result in an intestinal duplication The duplicate bowel characteristically lies on the mesenteric side of the adjacent bowel between the leaves of the mesen tery In most instances the duplicate bowel communicates with the normal bowel either at one or both ends Rarely however it may remain entirely separate within the mesentery and is then re ferred to as an enterogenous cyst. One can readily distinguish this cyst from other types of mesenteric cysts by the fact that its histologic structure is iden tical to that of adjacent bowel.

2. Cysts arising from Meckel s diver ticulum Here too, the cysts, which oc cur in relation to the distal portion of the ileum, are located on the antimesenteric side of the bowel. They do not concern us in this discussion

Traumatic blood cysts are mentioned for the sake of completeness. They gen erally result from injury causing a hema toma to form either within the various mesenteries or in the retroperitoneal tis sues

FIBROBLASTIC TUMORS

Incidence

Fibrous tissue tumors arising in the retroperitoneal space are rare, although their presence in the mesentery has been recorded with greater frequency It is difficult to determine the exact incidence of this tumor in the retroperitoneum from reported series because of the use of conflicting terms

Andrews in 1923 studied 28 primary retroperitoneal sarcomas from the Mayo Clinic and classified five as fibrosarcomas one as fibromyosarcoma, and five as spindle-cell sarcomas In the 107 retroperitoneal tumors which Frank collected from the literature (1925 to 1936) there were eight fibromas, five fibrosarcomas, three fibromyomas four fibromyosarcomas, and five spindle-cell sarcomas In the 17 cases reported by Hansmann and Budd only two were fibrosarcomas Mc Namara and Boswell in 1940 found eight retroperitoneal connective tissue tumors in the course of 2500 routine autopsies In 1946 Donnelly reported 19 fibrosarcomas among 95 retroperitoneal tumors Stout in 1948 reported 218 cases of fibrosarcoma, of which six occurred in the mesentery and two in the retroperitoneum. He thoroughly reviewed the lit erature in search of cases occurring in the mesentery omentum, and retroperi toneal region but was unable to accept the diagnosis in many instances because they were reported as spindle-cell sar coma and lacked adequate histologic de scription

Pathology

The gross and microscopic features of retroperitoneal tumors of fibroblastic ori gin are not significantly different from those occurring more commonly in other locations

Metastases from Retroperitoneal Fibrosarcomas

Of eight retroperitoneal fibrosarcomas reported by McNamara *et al.* two metastasized, to the lungs in one instance, and to the skeleton, liver and regional nodes in the other

Diagnosis, Treatment, and Prognosis

There are no characteristic symptoms and physical findings sufficiently pathognomonic to insure the preoperative identification of a fibroblastic tumor This diagnosis should be considered if the retroperitoneal tumor exhibits slow, insidious growth with minimal symptoms in a middle-aged patient The final diagnosis of fibrosarcoma is made only after careful histologic examination

Surgical eradication is the treatment of choice. There is a high incidence of recurrences Radical surgery is difficult to perform in the retroperitoneal space, but one must attempt to excise not only the tumor itself but also a margin of apparently healthy-appearing tissue on all sides. Postoperative x-ray therapy is indicated whenever the margin of excision is not considered adequate or tumor tissue is known to have been left behind.

Fibrosarcomas have a cure rate which is favorably high However, the prognosis appears to be much worse than for the same tumor found elsewhere in the body, due in part to the late recognition of the tumor and to its location

MYXOMATOUS TUMORS

Myxoma is a tumor composed of stellate cells having long, anastomosing branches set in a homogeneous mucinous substance which stains with mucicarmine Inasmuch as mucoid tissue is not a normal component of adult tissue and resembles the primitive mesenchyme found in the developing embryo, it was assumed by Ewing that myxoma in the adult arises from islands or nests of such embryonal tissue The present confusion arises from the fact that many sarcomas, such as the liposarcomas, fibrosarcomas, and chondrosarcomas, may be composed of admixtures of myxoid tissue This change is interpreted by some to represent a secondary degenerative process within the tumor which in no



Fig 450 Retroperitoneal myxoma (Pack and Tabah, Surg Gynec & Obst 99 209, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)



Fig 451 Lateral view of retroperitoneal myxoma shown in Fig 450 (Pack and Tabah, Surg Gynec & Obst 99 209, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)

way affects the nature or behavior of the tumor

INCIDENCE

Stout reported 49 cases of myxoma and added 95 cases from the literature exclusive of those affecting the heart. Of this group of 144 cases five were retroperitoneal in origin. The largest myxoma of this entire group weighing over 5400 gm. was removed from the retroperitoneal region of a 36-year-old female.

TREATMENT

Surgical excision is the most effective form of treatment. If complete extirpation is not effected, the tumor will undoubtedly recur and may eventually kill the patient through its effects on adjacent organs and tissues The myxomas are only slightly radiosensitive therefore, radiation therapy is reserved for those tumors which are not amenable to surgical resection and for postoperative use.

TUMORS OF ADIPOSE TISSUE

ORIGIN AND INCIDENCE

In this series, there were 17 liposarcomas and 2 lipomas Ockuly and Douglass estimate that approximately 35 per cent of the retroperitoneal lipomas are of perirenal origin and that the right and left kidney regions are equally affected. The largest collection of retroperitoneal fat occurs around the kidney a fact which explains the high incidence of fatty tumors in this location.

CLINICAL FEATURES

Retroperitoneal fatty tumors occur more frequently in females than in males Lacene reported 70 per cent females Adair Pack, and Farrior reported 73 per cent females They occur in patients of all ages, but are observed most frequently in patients between the ages of 40 and 60 years Farbman estimated that approximately 300 cases of retroperitoneal lipoblastic tumors had been reported prior to 1950

These tumors are characteristically silent during their early growth. They grow slowly and are capable of attaining tremendous size. They generally make their presence known by reason of their great size, which causes progressive swelling of the abdomen, a palpable mass and later pain They may compress adjacent organs resulting in related symptoms The larger and more malignant tumors may cause weight loss, anorexia, and asthenia.

PATHOLOGIC FEATURES

In the past the majority of these tumors were believed to be benign and large series of retroperitoneal lipomas were reported. With the passage of time, many such tumors recurred, not once but as often as four or five times the recurrences were deemed to be sarcomatous It is now generally believed that the majority of benign appearing lipomas have definite foci of sarcomatous change within them, and that only by careful microscopic study are these sarcomatous portions more frequently discovered. Farbman found sarcomatous changes to occur in a higher percentage of cases than in the past, e.g 47 per cent in his series covering between 1937–47 as compared with 14 per cent in von Wahlendorf's study in 1921 In our group of 19 cases there were only two lipomas, the remainder being classified as liposarcomas Stout is of the opinion that the majority of liposarcomas originate as malignant tumors and that only rarely does a benign lipoma become malignant

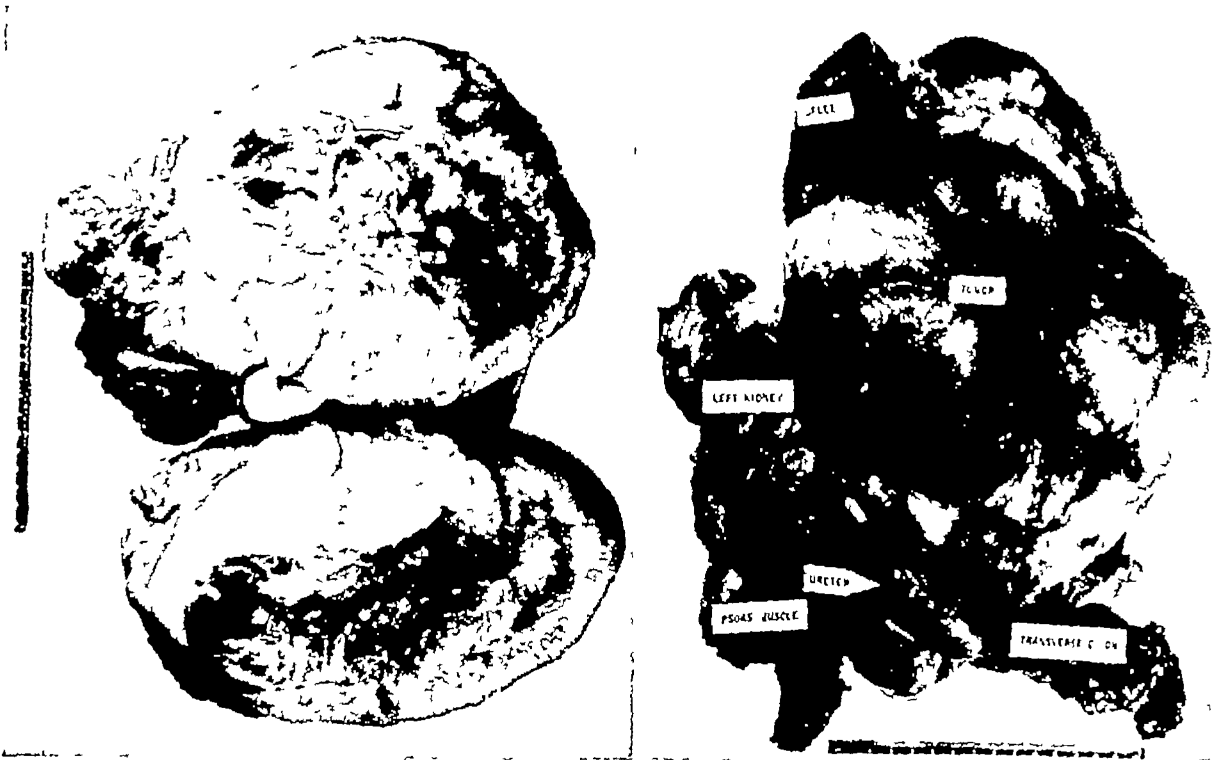


FIG 452 Retroperitoneal liposarcoma Two views of gross specimen, illustrating the relationship of the tumor to the contiguous resected normal tissues (Pack and Tabah, Surg Gynec & Obst 99 209, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)

DIAGNOSIS, TREATMENT, AND PROGNOSIS

Windholz took advantage of the low specific gravity of fat and its lesser coefficient of absorption as compared with surrounding structures to show the lipoma as a translucent body in the roentgenogram Taking water as having an absorption coefficient of 1, the corresponding value of fat is approximately 0 486 The larger the tumor the greater is said to be the contrast in radiolucency A retroperitoneal lipoblastic tumor can be distinguished from other tumors of this site by its translucency in the roentgenograph Everett and Fink found two conditions under which lipomas may not be visualized on the x-ray film: (1) the stroma may contain so much water that the absorption ratio approximates tha

TABLE 101 END RESULTS IN THE TREATMENT OF RETROPERITONEAL LIPOSARCOMA

	Patients Who Had No Previous Treatment			*Patients Who Had Previous Treatment*		
End Results	*Number*	*Postoperative Duration*	*Duration from First Symptom*	*Number*	*Postoperative Duration*	*Duration from First Symptom*
Dead from neoplasm	3	3, 32, and 75 mos	4 and 68 mos , 13 yrs	5	2, 3, 4, 9 108 [illegible]	7, 11, 16, 11, 17 [illegible]
Died from other causes with neoplasm	2	13 and 62 mos	29 and 65 mos	—		

of water, (2) the tumor may lie upon normal tissues instead of displacing them and thus superimpose their shadows

The treatment of retroperitoneal lipomas and liposarcomas is operative excision Every effort should be made to remove the entire tumor X ray therapy is justified for frankly inoperable liposarcomas Our experience has proved that many liposarcomas, particularly the smaller and recurrent tumors, are radiosensitive Technically inoperable retroperitoneal liposarcomas have become resectable following preliminary radiation therapy

Without treatment the so-called benign lipomas will continue to grow and lead ultimately to death. With excision, although these tumors have a relatively high recurrence rate and a tendency to undergo sarcomatous changes cures may still be achieved and in the remainder good palliation can be expected. Life can sometimes be extended indefinitely by reoperating on bulky recurrent retroperitoneal liposarcomas although with the knowledge that total extirpation of the lesion is not possible because of its size or involvement of vital structures

SMOOTH MUSCLE TUMORS

The origin of smooth muscle tumors within the retroperitoneal space is not readily explicable. Structures containing smooth muscle, such as the blood vessels spermatic cord, and embryonic wolffian duct and müllerian-duct remnants are found in the retroperitoneum and conceivably could be the source of these tumors

Incidence

Retroperitoneal smooth muscle tumors are relatively rare Golden and Stout collected nine cases of retroperitoneal smooth muscle tumors of which six were malignant and three were benign. In Donnelly's report of 95 retroperitoneal tumors, there was not a single instance of leiomyoma or leiomyosarcoma. Newman and Pinck had one case of leiomyosarcoma in their group of 33 retroperitoneal tumors

Clinical and Pathologic Features

The smooth-muscle neoplasms in the retroperitoneal region are capable of reaching a large size in contradistinction to the smaller leiomyomatous tumors found in the gastrointestinal tract. In four of our seven patients the initial symptom which prompted the patient to seek medical attention was abdominal pain In six of our seven patients the adjacent organs were involved by the tumor

The tumor is usually lobulated and well circumscribed by a pseudocapsule from condensation of the more peripheral tumor tissue. Cyst formation, hemorrhage, necrosis and calcification occur within the larger tumors It is sometimes necessary to evacuate the cysts either wholly or partially in order to facilitate operative removal.

Metastasis

Metastasis by the blood stream from retroperitoneal leiomyosarcomas was first recorded by Stout in three cases The liver lungs and peritoneum are the favorite sites of secondary deposit Metastases occur with greater frequency from retroperitoneal leiomyosarcomas than from those primary in the gastrointestinal tract, perhaps because of their longer duration and greater size before giving rise to alerting symptoms Metastases to lymph nodes have not been recorded from a retroperitoneal leiomyosarcoma

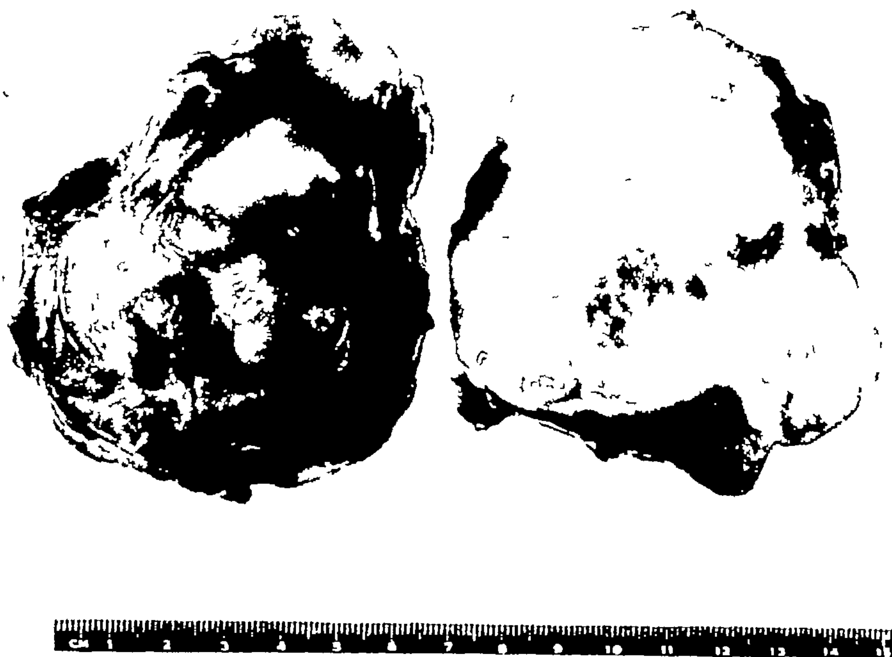


FIG 453 Retroperitoneal leiomyosarcoma Gross specimen Note lobulation of the surface and dense consistency of the cut section (Pack and Tabah, Surg Gynec & Obst 99 209, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)

TREATMENT

The proper treatment is complete surgical excision Because these tumors may infiltrate adjacent organs it may be necessary to resect portions of those viscera in order to remove the neoplasms in their entirety In our group of 5 patients who had undergone radical surgery there was 1 postoperative death, a 20 per cent mortality Of these 5 patients, 3 had leiomyosarcomas and 2 leiomyomas If complete removal cannot be achieved an intensive course of postoperative x-ray therapy should be given Such treatment will produce temporary palliation and in some instances many years of comfortable life

STRIATED-MUSCLE TUMORS (RHABDOMYOSARCOMA)

This series of 22 retroperitoneal rhabdomyosarcomas represents the largest reported group of such tumors occurring in this region Of 121 cases of rhabdomyosarcoma reported by Stout, only one arose retroperitoneally (Tourneux and Gouzi in 1932) Each of our 22 cases was classified by our pathologist either as embryonal rhabdomyosarcoma or rhabdomyosarcoma (adult type)

EMBRYONAL RHABDOMYOSARCOMA

Of the 22 retroperitoneal rhabdomyosarcomas, 7 were classified as embryonal rhabdomyosarcomas The age of these patients varied from 5 months to 10 years, the average being 5 years There were 4 males and 3 females The initial evidence was abdominal pain (2 cases), pain radiating down the thigh and the leg (3 cases), and the presence of an abdominal mass (2 cases) The finding of an abdominal mass was recorded in all patients The exact site of the tumor was listed as follows left lower quadrant, 2 cases, right midabdomen, 1 case, lower abdomen, 1 case, lower abdomen and pelvis, 1 case The size of the tumor varied from 11 to 20 cm. The neoplasm involved adjacent organs and major blood vessels in five instances Metastases occurred by the blood vascular and lymphatic routes to lungs, liver, and regional lymph nodes



Fig 454. Retroperitoneal embryonal rhabdomyosarcoma. (*Upper*) Gross specimen. Note necrotic, hemorrhagic regions characteristic of rhabdomyosarcoma. (*Lower*) Histologic characteristics of a cellular embryonal rhabdomyosarcoma. (Pack and Tabah, Surg. Gynec. & Obst. 99 313, 1954. *Courtesy* Surgery Gynecology and Obstetrics.)

All seven patients with embryonal rhabdomyosarcoma had had previous operations elsewhere in only two cases was the tumor excised, both incompletely Treatment at the Memorial Hospital was by exploratory laparotomy biopsy and postoperative x ray therapy successful in five cases. Two patients had radical excision, with one dead of recurrence within 6 months and one living and well less than 1 year

Adult Rhabdomyosarcoma

The retroperitoneal rhabdomyosarcomas in adults developed between the ages of 16 and 74 years (average 50.2 years) The sex ratio was 11 females to 4 males The size of the tumor varied from 6 to 20 cm. in diameter In 10 patients *no metastases* occurred. There were metastases to the lungs in two cases, to the regional lymph nodes in

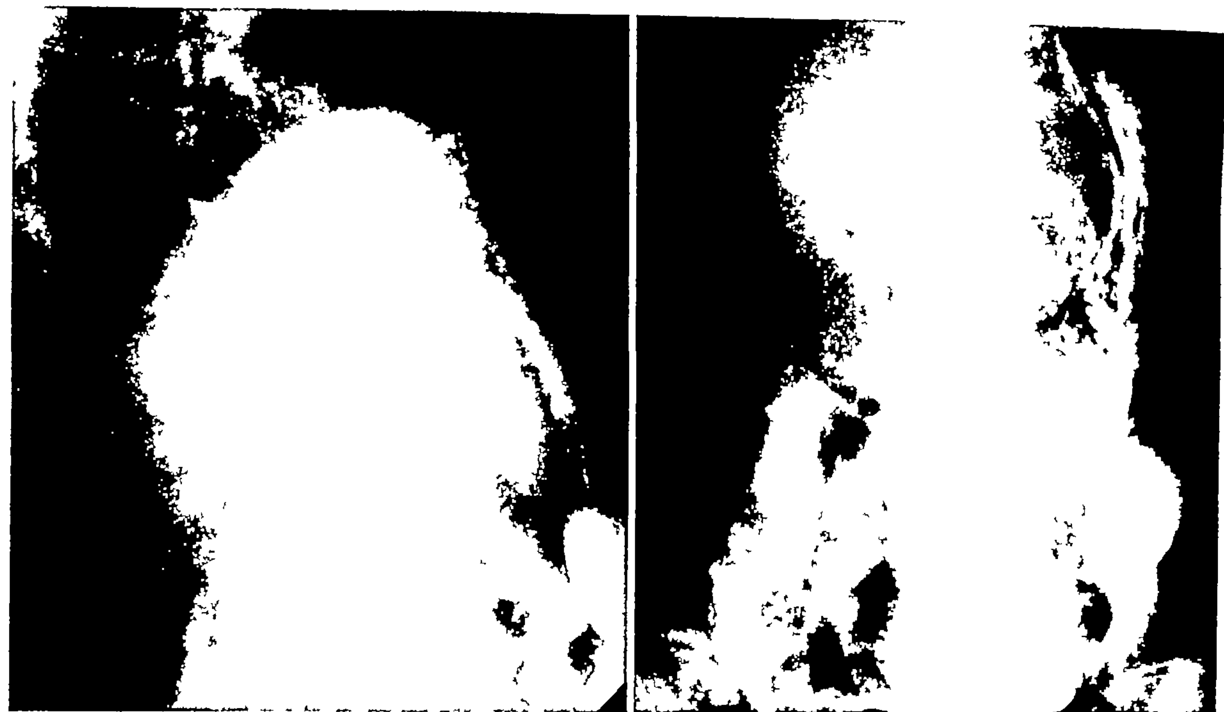


FIG 455 Retroperitoneal rhabdomyosarcoma, two different patients (*Left*) Anterior displacement of stomach, seen on lateral roentgenogram (*Right*) Left lateral displacement of stomach by the tumor (Pack and Tabah, Surg Gynec & Obst 99 313, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)

two cases, and in one patient widespread metastatic deposits were found in the omentum and peritoneum

Six patients had had no treatment elsewhere For the others the previous treatment was exploratory laparotomy, 6, exploratory laparotomy, biopsy, and x-ray therapy, 4, partial excision, 2, and radical excision, 4

TREATMENT

The only treatment, as for other retroperitoneal tumors, is radical surgical removal The results of treatment have been poor, the only hope of improving results is to secure the patients earlier and to attack the tumors more vigorously Sixteen patients in this series had previous operative procedures, four whose tumors were declared inoperable were later successfully operated on, by very radical procedures

Of the 17 patients explored or autopsied, all had fixation or infiltration of adjacent organs by the tumor, twelve growths were adherent to major blood vessels

END RESULTS

The end results of our 22 cases are briefly summarized in Table 102

TABLE 102 SUMMARY OF 22 CASES OF RETROPERITONEAL RHABDOMYOSARCOMA

End Result	*Number of Cases*	*Duration from Treatment*	*Duration from Onset of First Symptom*
Postoperative deaths	2		Less than 1 month, 3 years
Dead from rhabdomyosarcoma	15	From 2 to 26 months	From 3 to 28 months
Living with rhabdomyosarcoma	4	3, 4, 5, and 7 months	9, 14, 24, and 65 months
Living without rhabdomyosarcoma	1	3 months	4 months

LYMPHOMAS

The retroperitoneal lymphomatous tumors were either lymphosarcoma or Hodgkin's disease The term *lymphosarcoma* is used in its broadest sense and includes the lymphocytic lymphoma, the reticulum-cell sarcoma, and the giant follicular lymphoma There were 24 such tumors in this series an incidence of 20 per cent constituting the largest single group of neoplasms of this regional distribution. The diagnosis in all cases was proved by histologic examination In 11 cases abdominal exploration had been done elsewhere In 14 cases the diagnosis was established by operative exposure and biopsy There were many additional patients in whom the diagnosis had previously been established by the presence of lymphomas in other regions of the body and who subsequently developed signs and symptoms of an abdominal tumor These patients were excluded from the present discussion because the intraabdominal finding was only one of the many manifestations of the lymphomatous tumor

Of the 24 retroperitoneal lymphomas 18 were lymphosarcomas and six were Hodgkin's disease. This incidence is not great among 2000 cases of lymphosarcoma and 1000 cases of Hodgkin's disease on file at the Memorial Cancer Center





FIG. 458 (*Upper*) Giant follicular lymphoma of small bowel mesentery (*Lower*) Obstruction and lymph stasis in mesenteric lymphatics due to large tumor (xanthogranuloma) at base of mesentery (Pack and Tabah, Surg Gynec. & Obst. 99 313 1954 *Courtesy* Surgery Gynecology and Obstetrics.)

TUMORS OF THE SYMPATHETIC GANGLIA

GANGLIONEUROMA AND NEUROBLASTOMA

Tumors developing from the sympathetic ganglia include the paraganglioma, ganglioneuroma and the neuroblastoma (see Chap 23)

In his study of 32 cases of abdominal neuroblastoma Farber found that the primary tumor arose from the adrenal gland in 13 cases and from other retroperitoneal tissues in 19 cases Scott and Palmer in 1932 reviewed only those cases of sympathicoblastoma arising in the cells of the sympathetic system other than those occurring within the medulla of the adrenal gland. They collected 18 cases of completely undifferentiated neuroblastoma from the literature, of which seven occurred in the retroperitoneal region of the abdomen and one in the pelvis there were also 13 cases of differen

tiated sympathetic neuroblastoma, of which 8 were retroperitoneal in the abdomen and 2 in the pelvis.

McFarland and Sappington reviewed 127 cases of ganglioneuroma up to 1935 Of this group, 26 occurred in the retroperitoneal region of the abdomen and 8 in the retroperitoneal region of the pelvis independently of the adrenal glands Five others arose from within the mesentery of the small bowel and only 16 were observed to have arisen from the adrenal glands. The remainder arose from sympathetic ganglia in other regions of the body

Willis estimates that the adrenal glands are the most frequent single site of origin of these tumors, accounting for about one-third of the cases, the abdominal and pelvic sympathetic chain (including the celiac and mesenteric ganglia) account for another one-third of the tumors, the remaining one-third is said to occur in the cervical and thoracic portions of the sympathetic chain together with small peripheral ganglia situated in the viscera themselves Our series includes 4 cases of neuroblastoma and 1 of ganglioneuroma which arose in the retroperitoneal sympathetic nervous tissues independently of the adrenal glands

Age and Sex

The majority of reported neuroblastomas occurred before the age of 4 years The average age in our series was 3 1 years with the extremes being 3 months

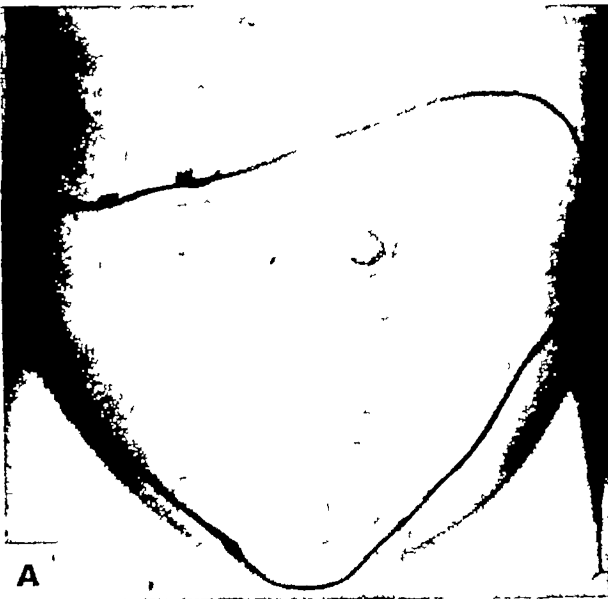








Fig 457 Extraadrenal neuroblastoma, two different patients A Location of recurrent tumor in young girl B Deviation of left ureter by extraadrenal neuroblastoma shown in A C Extrinsic pressure on stomach by large upper abdominal neuroblastoma D Downward displacement of transverse colon by tumor shown in C (Pack and Tabah, Surg Gynec & Obst 99 313, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics)

and 9 years. While ganglioneuromas may appear during early childhood, in the *majority* of cases they do not appear until slightly later in life. Most of the reported series show no sex predilection for neuroblastoma or ganglioneuroma.

Pathologic Anatomy

Growth of the tumor is continuous and involvement of adjacent organs either by direct infiltration or by pressure is quite frequent. The tumor may insinuate itself through the intervertebral foramina to cause pressure on the spinal cord and produce paraplegia

Metastasis

Local extension and direct infiltration of contiguous organs is the most common route of spread. Metastasis by means of the lymphatics is the next most common method, whereas blood stream metastasis, although the most serious is third in frequency The wide dissemination of metastases observed with this tumor accounts for the poor end results of treatment.

Sometimes we are defeated in attempts at surgical extirpation of a well differentiated and localized ganglioneuroma, or even a neuroblastoma, because the tumor has intimately associated itself with a major and vital blood vessel or organ or has extended through an intervertebral foramen to cause compression of the cord.

Symptoms

The presenting signs and symptoms generally occur because of metastasis to distant organs and tissues The primary focus of the lesion may remain symptomatically silent but not infrequently it presents itself as a progressively enlarging abdominal mass In young children and infants, fever and gastrointestinal symptoms including vomiting, diarrhea and loss of weight may be the main features causing the mother to seek medical attention for her child.

Ecchymosis of the eyelids, with or without proptosis, symptoms referable to the lower extremities including pain, swelling, or limping, enlarged cervical or inguinal lymph nodes, urinary symptoms anemia—any one or a combination of two or more of these findings may herald the clinical onset of the disease.

Treatment

In neuroblastoma the earlier the diagnosis and the more aggressive the treatment, the better are the prospects of cure. Although the majority of neuroblastomas are radiosensitive, irradiation alone has proved to be very disappointing. Nevertheless, treatment with irradiation has produced some wonderful palliative effects in inoperable or nonresectable cases, such as marked shrinkage and in some cases complete disappearance of the tumor mass and a general systemic improvement with relief of pain and increase in appetite and strength. A combination of surgical excision and immediate postoperative irradiation is probably the best plan of therapy today

With ganglioneuroma, particularly the well-differentiated variety the treatment of choice is radical surgical excision, which will usually result in cure. Should it not be possible to remove the lesion in its entirety because of its location, one is nevertheless justified in removing as much of it as possible without jeopardizing the patient's life. The tumor is slow growing and it may be many years before recurrences reach a sufficient size to require further resection With the less well-differentiated ganglioneuroma, the treatment should be similar to that outlined for neuroblastoma.

EXTRAADRENAL PARAGANGLIOMA

About 90 per cent of pheochromocytomas are said to occur in the adrenal glands, with the right being involved slightly more frequently than the left According to Maier, approximately 200 adrenal tumors have been recorded in the literature, and only 19 cases of extra-adrenal tumors, three of which were located in the chest Brines and Jennings, and Richards and Hatch report that 11 of the retroperitoneal extraadrenal tumors have occurred in the organ of Zuckerkandl (which is situated just above the bifurcation of the aorta), 3 at the hilus of the kidney, and 2 others within the retroperitoneal area We may conclude that the incidence is about once for every 10 cases arising in the adrenal glands, and if we confine it to the retroperitoneal space this incidence drops slightly to about 1 in 12 cases These extraadrenal paragangliomas, like those occurring in the medulla, may or may not be physiologically active When active, the disturbances resulting are identical to the pheochromocytomas In about 10 per cent of the cases, the tumors are multiple, and of the 210 cases reviewed by Brines and Jennings there were 18 in which both adrenal glands were involved Multiple tumors in the retroperitoneal region only, or in the retroperitoneal region and the adrenal gland, have been reported

Treatment

The only known treatment of these tumors is complete surgical excision In most instances a preoperative localization of the tumor is possible Generally speaking, the usual kidney incision combined with a resection of the twelfth rib is adequate In cases where one is unable to locate the exact site of the lesion it is perhaps best to use a transperitoneal approach utilizing a vertical or transverse incision In addition to exploring both adrenal regions one must also explore carefully the region of the sympathetic nerve trunks, the hilar region of the kidneys, and the lower aorta Grimson prefers to use a transthoracic approach through the bed of the eleventh rib and through the diaphragm The left side is done first and the abdomen is explored If the tumor is not located on this side a similar transthoracic, transdiaphragmatic retroperitoneal approach is made through the right eleventh-rib bed

The proper management of the patients before, during, and after surgery is of vital importance The removal of nonfunctioning tumors is generally nothing more than a technical procedure With the functioning paragangliomas, however, the difficulties are many times greater (See Chap 23)

CASE REPORT NO 82 RETROPERITONEAL PHEOCHROMOCYTOMA (EXTRAADRENAL PARAGANGLIOMA)

F W , a 61-year-old woman, was in good health until approximately 50 years of age, at which time a thyroidectomy was done elsewhere because of the presence of an intrathoracic goiter associated with episodes of difficult breathing, profuse sweating, and a weight loss of 25–30 lbs The symptoms occurred intermittently and were not relieved by the operation She was given thyroid extract postoperatively but this was discontinued because of a progressively increasing blood pressure Two years prior to this examination she had complained of postprandial fullness and indigestion Radiographic studies of the stomach made at various times before and after dietary management showed a possible ulcer on the posterior wall of the pars media, but this defect always disappeared under medical management Gastric analysis revealed complete anacidity following the administration of histamine Gastroscopy showed a questionable induration of the gastric wall without definite ulceration Occult blood was constantly present in the stools Quantita

tive blood sugar estimations varied from 158 to 228 mg per cent. The blood urea nitrogen was within normal limits

Treatment

An exploratory laparotomy was done and when the stomach was palpated the patient went into shock on the operating table during which time the blood pressure dropped to 70/40 millimeters of mercury No abnormality in the stomach was discovered on palpation The operation was temporarily halted until the patient recovered from shock. On palpating the small intestines gently a second episode of severe shock occurred so the operation was abandoned.

The patient died within 12 hours following the operation, and preceding death was in collapse with a temperature of 103 F a pulse of 140 and clinical and electrocardiographic evidence of acute cardiac decompensation

Pathologic Report

Postmortem examination revealed an oval shaped, lobulated circumscribed tumor in the retroperitoneal tissues between the lower pole of the left kidney and the aorta. The external surface of the tumor was lobulated and thinly encapsulated Prominent blood vessels were seen on the capsular surface Small areas of hemorrhage were found on cut section of the tumor (Fig 458.)

Under the microscope, the tumor consisted of nests of well-differentiated cells in an alveolar arrangement In the septa were numerous small capillaries In addition numerous large veinlike channels were present, several containing recent partially organized thrombi. The tumor cells had abundant acidophilic cytoplasm

Final diagnosis Retroperitoneal pheochromocytoma (benign) extrasuprarenal.

Comment

The tumor was not suspected preoperatively It may have been a functioning pheochromocytoma and could have accounted in part for the symptoms of which



FIG. 458. Extraadrenal pheochromocytoma. Gross specimen illustrating the typical appearance of pheochromocytoma. The tumor was yellow brown in color (Case report No 82.) (Pack and Tabah, Surg. Gynec. & Obst 99 313 1954 *Courtesy* Surgery Gynecology and Obstetrics.)

the patient complained The shocklike episodes occurring in the course of the abdominal exploration may have been due to inadvertent massage of the tumor

This case is interesting from several points of view First of all, this patient presented none of the classical clinical symptoms or signs suggestive of episodes of paroxysmal hypertension Even after the diagnosis was histologically established her preoperative symptoms were carefully reviewed with the patient and again a specific history was never established. Her main reason for seeking medical attention was because of a sense of pressure in her right upper abdomen and pain in her back. This mass was massaged repeatedly during her many physical examinations but massage never resulted in discomfort to the patient or gave rise to episodes suggestive of paroxysmal hypertension. Again, during the operation the tumor was not handled with the gentle respect one would ordinarily give such a lesion, merely because the possibility of the diagnosis was never considered. Yet in spite of this she did not go into the typical hypertensive reaction described in the literature. Postoperatively her blood pressure equaled the preoperative reading From the above we can conclude that this

tendency to invade bone by direct extension and by its ability to recur following surgical excision It can metastasize both to regional lymph nodes and to distant viscera

The diagnosis of a sacrococcygeal chordoma will rarely present much difficulty It either produces a bulky mass externally or within the hollow of the sacrum When the growth tendency is posterior, the sacrum is invaded and destroyed relatively early in the disease, and x-ray studies of this region will usually show evidence of bone destruction

When the direction of growth is anterior, it will eventually result in a pelvic mass and in the late stages a retroperitoneal intra-abdominal tumor will become obvious Diagnosis then becomes more difficult and one may be unable to differentiate it from any one of the retroperitoneal tumors which can extend into the pelvis It is also conceivable that a chordoma will present itself entirely as an abdominal retroperitoneal mass, having arisen either from the lumbar or lower thoracic vertebrae This occurs in approximately 5 to 10 per cent of all chordomas

CASE REPORT NO 87
RETROPERITONEAL CHORDOMA

A 39-year-old white female first experienced lower abdominal pain one month prior to her admission to the Memorial Hospital In addition she noted progressive enlargement of her abdomen Her appetite was poor and she had had recent episodes of hematuria On physical examination she was found to have a large mass occupying the entire left half of the abdomen It extended from the left costal margin to 4 fingerbreadths above the symphysis pubis and medially as far as the midline Pelvic and rectal examinations and x-ray of the chest were normal Films of the lumbosacral spine with special demonstration of the sacrum showed no evidence of bone disease or destruction A barium enema revealed evidence of extrinsic pressure on the descending colon A retrograde pyelogram showed a large abdominal mass causing upward and medial distortion of the left kidney and medial displacement of the left ureter

Surgical exploration resulted in the preoperative diagnosis of renal tumor A tremendous neoplasm was found arising from the retroperitoneal space and occupying almost the entire left side of the abdomen The spleen was normal The kidney was displaced upward and medially and the descending colon was fixed over the growth, which invaded the abdominal wall laterally and posteriorly There were several smaller implants from 1 to 1 5 cm in diameter within the mesentery and in the pelvis Biopsy of the tumor and one of the implants was performed The microscopic diagnosis was chordoma She received a course of deep x-ray therapy to the left upper and lower abdomen, but the tumor continued to increase slowly in size and she died 2 months after surgery

RETROPERITONEAL MALIGNANT NEURILEMMOMA (SCHWANNOMA)

There were two cases of retroperitoneal malignant neurilemmoma and one of benign neurilemmoma (Fig 460)

CASE REPORT NO 88
RETROPERITONEAL MALIGNANT NEURILEMMOMA

A 5-year-old white female was first seen in June, 1950 One month before, while she was under treatment for pneumonia at another hospital, a flat plate of the abdomen revealed the presence of a tumor in the pelvis She was referred to the Memorial Hospital when the tumor proved to be inoperable

On admission, a hard, smooth, fixed pelvic mass was palpated on rectal examination Surgical exploration disclosed a 6 × 5 cm tumor, fairly well circumscribed and encapsulated, which was occupying the retroperitoneal space of the left iliac fossa The complete removal of this tumor was most



Fig. 460 Retroperitoneal benign schwannoma. Gross specimen (two views) demonstrating complete encapsulation of the tumor (Pack and Tabah Surg Gynec. & Obst. 99 313 1954. *Courtesy* Surgery Gynecology and Obstetrics.)

difficult because of the previous operation and adhesions to numerous pelvic structures A two-stage procedure was required to remove the tumor in toto but injury to the lumbosacral plexus left some weakness in the left foot. The diagnosis was malignant neurilemmoma The patient remains well 7 years later

RETROPERITONEAL XANTHOGRANULOMA

In 1935 Oberling described a tumor having histologic characteristics of both a granuloma and an xanthoma which he named *xanthogranuloma* He reported 3 cases and collected 3 additional cases from the literature. Although it was capable of occurring in various regions of the body the retroperitoneal xanthogranuloma represented a very characteristic localization of this tumor In this location the tumor is capable of reaching a considerable size As a rule adjacent organs such as kidneys adrenals, pancreas etc become enclosed in the granulomatous tissue but in spite of its supposedly benign aspects this lesion is capable of local invasion and destruction. Growth is characteristically slow but progressive Recurrences are frequent and death can occur either from its local or generalized effect Oberling quotes the case of the patient reported by Noel and Michel-Bechet, who 4 years after resection of a retroperitoneal xanthogranuloma died of massive local recurrence with uremia. The cases reported by Dietrich and by Nother are also quoted by Oberling as being examples of xanthogranuloma, and yet both of these at autopsy were found to have (in addition to the main retroperitoneal mass) similar small nodules involving the liver lungs spleen peritoneum etc. He states that an interesting feature of this tumor is its ability to develop metastasislike lesions at a distance, such as in the peritoneum and viscera. He considers that these lesions are related to the Hand Schüller Christian disease and that the tumor may be of multicentric origin

The etiology and pathogenesis of this condition are unknown Oberling concluded that two factors are at work in its pathogenesis an inflammatory process and some disturbance of cholesterol metabolism.

The treatment of the lesion is surgical excision. Oberling advocates the use of postoperative x ray therapy to prevent recurrence

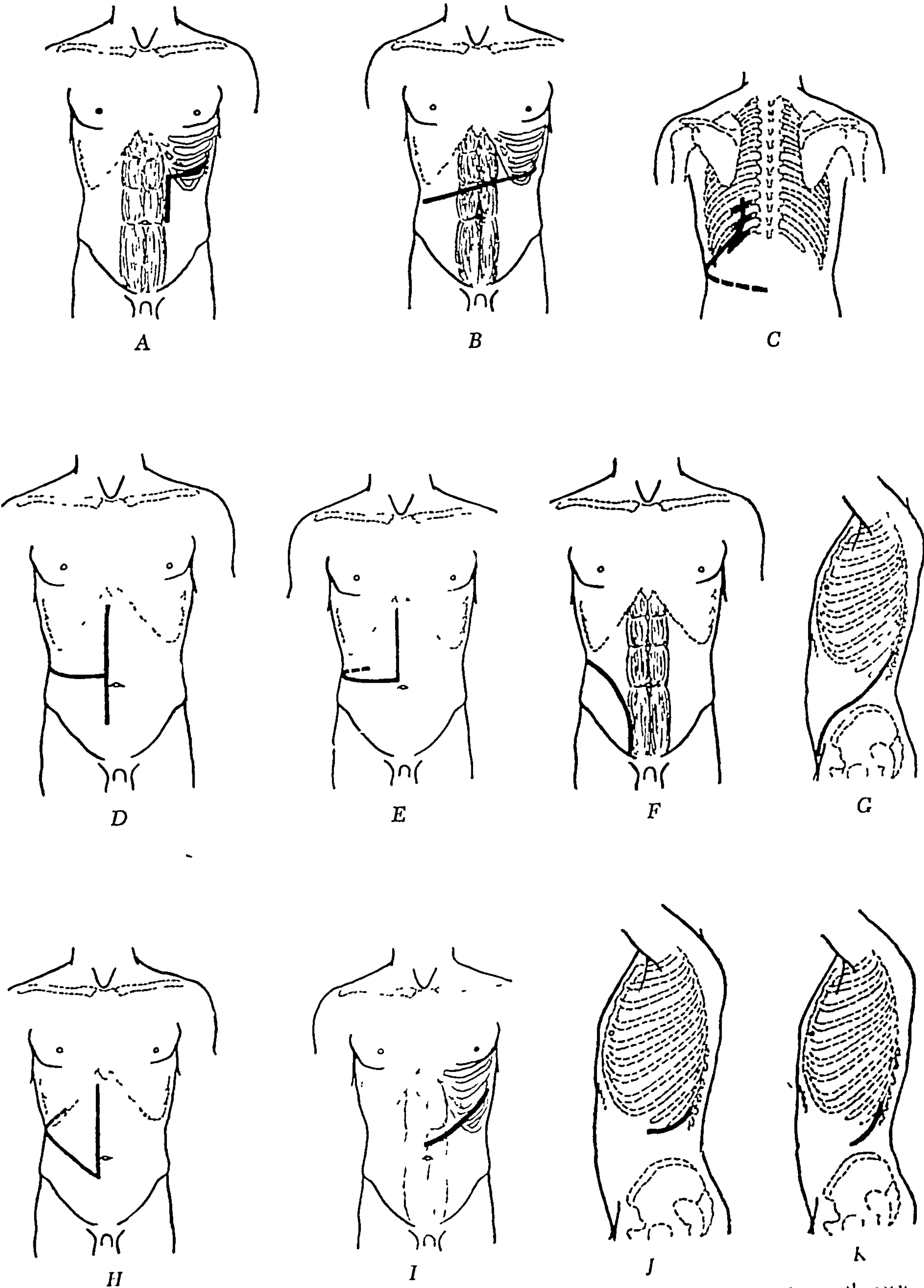


Fig 461 Incisions for exposure and removal of retroperitoneal tumors *A* Abdominothoracic incision (Garlock) *B* Abdominothoracic incision (employed by Pack and Tabah) *C* Dorsolumbar incision (Nagamatsu) *D* T-shaped incision (Young) *E* Extraperitoneal anterior incision (Cabot) *F* Abdominolumbar incision (Hinman) *G* Lumboilioinguinal incision (Morris) *H* Sweetser modification of Cabot incision *I* Abdominothoracic incision (Humphrey) *J* Oblique flank incision *K* Transverse flank incision (Pack and Tabah, Surg Gynec & Obst *99* 313, 1954 *Courtesy*, Surgery, Gynecology and Obstetrics.)

point of the iliac crest. The usual length of the incision is 6 to 8 inches but it may be enlarged by an anterior extension. The muscles are divided in the line of the incision down to the transversalis fascia. The fascia is opened to expose the perirenal fat or Gerota's capsule, the quadratus lumborum muscle, and the retroperitoneum.

TRANSVERSE FLANK INCISION

This commences like the oblique incision at the outer edge of the erector spinae but runs forward in a transverse direction across the flank. The deeper portions of the incision are similar to that described above. The exposure with these two incisions is rather limited and, except for smaller tumors situated in the perirenal region, the approach leaves much to be desired. Its principal advantage lies in the very low mortality and morbidity

OBLIQUE FLANK INCISION COMBINED WITH RIB RESECTION (HESS INCISION)

The incision is made directly over the middle of the twelfth rib The rib is exposed in the usual manner and resected. The incision is extended through skin and muscle for an additional 1 to 2 inches anteriorly The transversalis fascia is opened, and the peritoneum is pushed forward. Posteriorly the transversalis fascia is further opened with the finger care being taken to reflect the pleura upward under the costal margin If the pleura is opened it can be repaired immediately by suture. This incision gives a wider exposure of the kidney and perirenal region.

CABOT INCISION

This is an extraperitoneal anterior right angled incision which can be done with the patient flat on his back. The incision consists of a horizontal limb commencing at the midline just above the umbilicus and extending transversely across the abdomen and the flank. The vertical limb of the incision extends upward close to the midline below the xiphoid. The incision goes through skin, muscle, and fascia only and the large triangular flap created is then retracted over the rib margin. The unopened peritoneum is pushed medially The incision affords wide and excellent exposure for tumors in the lumbar region.

SWEETSER MODIFICATION OF THE CABOT INCISION

More recently Sweetser modified Cabot's approach by placing the patient in the lateral position. The usual oblique incision in the flank is made, through which the retroperitoneum or kidney can be explored. Having decided to resect the tumor the incision is extended downward and forward across the rectus muscle to a point in the midline halfway between the umbilicus and the symphysis pubis The vertical limb of the incision is similar to Cabot's The abdominal wall and the abdominal contents enclosed in the peritoneum fall away by gravity toward the opposite side, exposing the retroperitoneal space on that side. The advantage of this incision over Cabot's is that it does not cut across one or more nerve trunks of the abdominal wall.

HINMAN INCISION AND MORRIS INCISION

Both incisions are particularly useful for extensive lumbar tumors extending down into the lower abdomen or pelvis Hinman's incision was originally designed for retroperitoneal lumbar and pelvic lymph-node dissection for teratomas of the testis. The patient is placed flat on his back and the incision commences at the lower outer border of the rectus muscle and extends upward for

some distance along the edge of the rectus and then curves out to a point just below the tip of the twelfth rib and parallels the lower border of that rib for about half its length The fascia of the external oblique, internal oblique, transversalis, and latissimus dorsi muscles is divided in the line of the incision The peritoneum is stripped medially to expose the retroperitoneal space One can expose in succession the psoas muscle, with the ureter over it, the lower pole of the kidney, the aorta, and the inferior vena cava In the pelvis the common iliac and the external and internal iliac vessels can be readily visualized

THE MORRIS (OR LUMBOILIOINGUINAL) APPROACH

This affords a similar exposure of the retroperitoneal space as the one just described With this approach, however, the patient is supported at about 30 to 35 degrees on his good side The incision begins at the outer edge of the erector spinae muscle, just below the twelfth rib, and runs obliquely downward and forward to a point 1 inch internal to the anterior superior spine of the ilium The incision is continued 1 inch above and parallel to Poupart's ligament as far as the external ring The skin and muscles are divided to the peritoneum The latter is then reflected medially, using mainly blunt finger or gauze dissection, to expose the retroperitoneum This incision was originally designed to expose the entire length of the ureter, using a retroperitoneal approach

THE NAGAMATSU OR DORSOLUMBAR APPROACH

This is an extrapleural, extraperitoneal technic which allows an excellent exposure of tumors situated in the upper retroperitoneal paravertebral region It was originally designed for exposure of adrenal tumors and highly fixed kidneys, and removes the barrier of the lower ribs by excising short segments of the lower 3 ribs posterior to the angle This allows retraction upward of the lower thoracic cage, carrying with it the attached diaphragm and contained costophrenic angle Anteriorly the incision extends downward and forward, with the extent and direction depending upon the extent and position of the tumor The exposure is extrapleural and extraperitoneal and besides offering excellent exposure to the upper retroperitoneum is free from the danger of pleural or peritoneal contamination

TRANSPERITONEAL APPROACHES

The various incisions available for entering the peritoneal cavity are known to general surgeons and will not be discussed in detail The type of incision used will depend on the location and size of the mass It perhaps makes little difference whether one employs a transverse or vertical incision if the incision is adequate in length and optimum in position A very useful approach is Young's T-shaped transperitoneal incision, not unlike Cabot's or Sweetser's incision, the main difference being that the peritoneal cavity is entered

COMBINED ABDOMINOTHORACIC INCISIONS

The combined abdominothoracic incision is used with increasing frequency There is a slight increase in morbidity, consisting mainly of pleural effusion and intercostal neuralgia, but these are not serious and are greatly outweighed by the wider and unexcelled exposure The ease of exposure in turn allows a more rapid and thorough performance of the operation and this again more than compensates for the additional time required to make and close the incision

Humphrey's incision, reported in 1946, begins at the costal margin at the levels

of the eighth intercostal space and progresses to a point just to the right of the midline about 2 cm. above the umbilicus The left rectus muscle is divided. The *incision is then* continued through the eighth intercostal space to the posterior axillary line into the thorax, dividing the costal arch in the line of the incision. The diaphragm is split radially from its origin at the costal margin as far as the esophageal hiatus. It is rarely necessary to *split the diaphragm as far as* the esophagus inasmuch as one can stop 3 or 4 cm. short of that point without losing any of the advantages of the exposure.

Garlock begins his procedure with a 5-inch incision along the outer edge of the rectus muscle. The *incision is* then extended along the line of the eighth intercostal *space* The costal *margin is* divided as before and the diaphragm split partially down in a radial manner toward *the* esophageal hiatus

PREFERRED ABDOMINOTHORACIC INCISION

The incision we prefer extends obliquely across both sides of the abdomen at a slightly higher level and enters the chest through the ninth *intercostal* space. The incision begins about 2 inches *below the* rib *margin* on one side and runs obliquely upward toward the ninth intercostal space on the opposite side. The incision is continued through the costal margin at this point and up through the ninth intercostal space into the thorax. The diaphragm is split as described above By breaking the operating table a greater exposure of the upper abdomen is obtained.

SURGICAL PROCEDURE

After exposure of the retroperitoneum by one or another of the surgical approaches it is imperative to determine *whether the tumor is benign or malignant* prior to definitive surgery A frozen section will usually suffice to provide the answer although only rarely will the pathologist be able to give an exact histologic diagnosis If the tumor proves benign then naturally one would not *carry out a* procedure that might jeopardize the patient's life. The entire tumor should be removed if at all possible. Should the surgeon fail to determine beforehand whether a tumor is malignant and his efforts at surgical excision are inadequate, he has done that patient *irreparable harm* and the opportunity for cure is lost. Subsequent surgical attempts no matter how radical they may be will prove more difficult with less chance of success.

If the tumor proves to be malignant the surgeon can undertake a more extensive and radical *excision*, knowing full well that the only chance of cure in the majority of these tumors lies with this form of attack. This may entail partial bowel resection, nephrectomy partial *pancreatectomy splenectomy partial* gastrectomy and even partial hepatectomy The malignant retroperitoneal tumors are on the whole quite invasive and adherence or infiltration of adjacent structures is quite frequent.

It is significant that in 88 of our cases (71 6 per cent) the tumor infiltrated or was intimately adherent to adjacent organs In 10 cases there *was no involvement* of adjacent organs and in the remainder no mention of this fact was made. In 47 cases (39 per cent) one or other of the blood vessels (the aorta, inferior vena cava, renal, celiac, superior mesenteric, or one or more of the major pelvic *vessels*) were invaded or surrounded by tumor This finding was lacking in 41 cases (34 per cent) and not recorded in the remainder These two findings, the latter in particular were mainly responsible for the high percentage of inoperability

Certain blood vessels in the retroperitoneum can be sacrificed if necessary with little or no harmful effect to the patient. For example, the inferior vena cava may have to be ligated and excised; this is not fatal provided it is done below the level of the renal veins. On the other hand, intimate involvement of the renal pedicle on one side may necessitate sacrificing that kidney. Knowledge of the exact status and function of the opposite kidney is imperative. With involvement of the splenic vessels a splenectomy would naturally be indicated.

Not infrequently a major blood vessel becomes gradually occluded over a period of months by a progressively enlarging tumor. Under such circumstances adequate collateral vessels become established so that at surgery the tumor with the involved blood vessels can be sacrificed with impunity. This situation was seen in several of the cases where the tumor located in the pelvis obliterated the common or external iliac vessels, with little or no disability insofar as the circulation of the limb was concerned.

In the future improved results of treatment can be anticipated by a combination of earlier diagnosis, more aggressive surgery, and means of reconstruction or repairing major or vital blood vessels which may have to be sacrificed because of tumor involvement.

OPERABILITY AND RESECTABILITY OF RETROPERITONEAL TUMORS

In 59 cases (49 per cent) the patient sought medical advice within a period of 1 month after the onset of initial symptoms, and in 86 cases (71.8 per cent) the patients went to their doctor within the first 3 months. The remainder

TABLE 103. RADICAL SURGERY AT THE MEMORIAL HOSPITAL FOR MALIGNANT TUMORS CONSIDERED INOPERABLE ELSEWHERE

Histologic Type of Tumor	*Number of Cases*	*Survival Following the Operation at the Memorial Hospital*
Ganglioneuroma	1	Living without cancer 8 years*
Neuroblastoma	1	Died with cancer 10 months
Embryonal rhabdomyosarcoma	2	Died with cancer 6 months
		Living without cancer 3 months*
Rhabdomyosarcoma	2	Living with cancer 7 months
		Died with cancer 13 months
Leiomyosarcoma	3	Living without cancer 9 months
		Operative death
		Lost to follow-up with cancer 7 months†
Liposarcoma	2	Lost to follow-up with cancer 1 month*
		Living with cancer 6 months
Mesothelioma	1	Died with cancer 15 months
Malignant schwannoma	1	Living without cancer 18 months
Hemangiopericytoma	1	Living without cancer 12 months
TOTAL	14	5 living without cancer
		2 living with cancer
		2 lost to follow-up with cancer
		5 died with cancer

* X-ray therapy in addition given at the Memorial Hospital.
† Partial excision had been performed previously.

TABLE 104 MALIGNANT RETROPERITONEAL TUMORS
Summary of End Results

Histologic Type of Tumor	*Total Cases*	*Indeterminate Cases*	*Determinate Cases*	*Died with Cancer*	*Living with Cancer*	*Living without Cancer under 5 Yrs*	*Survival without Cancer 5 Yrs. or More*
Total cases	103	8	95	71	10	10	4
Rhabdomyosarcoma	22	0	22	17	4	1	0
Liposarcoma	17	0	17	11	4	2	0
Leiomyosarcoma	5	1	4	1	1	2	0
Lymphosarcoma	18	0	18	15	1	1	1*
Hodgkin s disease	6	0	6	6	0	0	0
Sarcoma of undetermined histogenesis	8	1	7	6	0	0	1†
Carcinoma	7	3	4	4	0	0	0
Fibrosarcoma	6	2	4	3	0	0	1‡
Neuroblastoma	4	0	4	3	0	1	0
Ganglioneuroma	1	0	1	0	0	0	1§
Mesothelioma	2	0	2	2	0	0	0
Myxoma	2	1	1	1	0	0	0
Malignant schwannoma	1	0	1	0	0	1	0
Hemangiopericytoma	1	0	1	0	0	1	0
Synovial sarcoma	1	0	1	1	0	0	0
Chordoma	1	0	1	1	0	0	0
Pheochromocytoma	1	0	1	0	0	1	0

* Lost tract of 13 years, without cancer
† Living, 8 years
‡ Lost tract of 6¼ years, without cancer
§ Indeterminate cases those lost track of under 5 years

sought advice at any time up to 2 years later Donnelly found the average duration of symptoms in his group of patients before they presented themselves for treatment was 9 4 months. In our group the delay averaged 4.2 months

The next delay occurred between the time the patient saw a doctor and the time treatment was begun. Of the 72 patients who received their initial treatment elsewhere this delay averaged 2.2 months and for 44 patients whose initial treatment took place at the Memorial Hospital it averaged slightly less than one month. Thus the total delay between the first symptom and the first treatment averaged from 5 to 6 months.

Andrews reported an operability rate of 7 4 per cent Judd and Larsen, in a review of 44 cases of retroperitoneal sarcoma, found an operability rate of 32 per cent. Donnelly reported a rate of 35 per cent, and Newman and Pinck 36.3 per cent.

Of the total of these 65 patients whose treatment elsewhere was known, 54 patients, or 83 per cent, had been considered inoperable (only partial excision of the tumor was possible or they were only explored and biopsied) or else had additional postoperative x ray therapy Three had x ray therapy alone. In only 11 patients (16 9 per cent) had total excision of the tumor been effected prior to admission. Of the remaining 54 patients with malignant tumors (who were seen subsequently at the Memorial Hospital) 30 underwent additional surgical exploration since there was not sufficient evidence to indicate absolute inoperabil

ity Of this group reexplored, it was possible to carry out total surgical excision of the tumor in 14 cases (46 7 per cent), a worthwhile effort (Table 103)

Local extension or metastasis to regional lymph nodes prevented resection in many of the patients

Of the 38 patients with malignant tumors (64 5 per cent) treated initially at the Memorial Hospital 30, or 78 9 per cent, had tumors which were considered either nonresectable on exploration or only partially resectable and then given x-ray therapy or no treatment at all In 21 1 per cent of the patients a definite attempt at curative surgical extirpation was done

INCIDENCE OF METASTASES FROM RETROPERITONEAL TUMORS

Metastases from the specific types of retroperitoneal tumors are recorded in the analysis of each group. Forty of our retroperitoneal tumors are known to have metastasized, an incidence of 33 3 per cent among the 120 cases In 49 patients there were no metastases and in the remainder it was not known whether metastasis had occurred or not, and if it had, specific mention of this fact was not recorded The majority of the patients in this last group had undergone surgical treatment elsewhere and were referred to the Memorial Hospital for radiation therapy

In our cases metastases occurred to lymph nodes in 11 cases, to the lungs in 9, to the liver in 6, and to multiple intraperitoneal sites (omentum, mesentery, and peritoneum) in 5 instances There were 9 additional cases showing multiple metastases to liver, lungs, bone, nodes, and other viscera, including spleen, kidney, pancreas, and spinal cord.

OPERATIVE MORTALITY RATE

The reported operative mortality following the removal of retroperitoneal tumors varies from 16 per cent to 25 per cent In the 107 cases reviewed by Frank there was an operative mortality of 18 4 per cent, Pemberton and McCoughan in a series of 42 cases reported a 20 per cent mortality, and von Wahlendorf in a series of 113 cases reported a 25 per cent mortality

In our group of patients there were 85 who underwent either primary or secondary surgical treatment at the Memorial Hospital Of this group there were 5 operative deaths and 4 delayed deaths which occurred while the patient was still in the hospital and within a period of 2 months after surgery This makes an operative mortality of 10 8 per cent, which is much lower than the quoted average

RADIATION THERAPY

Radiotherapy plays a definite part in the management of certain of these retroperitoneal tumors Although it rarely cures, palliation may be achieved, with resultant decrease in pain, increase in sense of well-being, and prolongation of life In general, the indications for irradiation are the following

1 Inoperable tumors Its use in cases of inoperable tumors is almost axiomatic since there is practically nothing else to offer It is often surprising to find good response by a tumor ordinarily considered to be radioresistant Large inoperable tumors may shrink sufficiently in size as to make removal possible, with less shock and operative mortality Donnelly found that in 22 patients treated by deep x-ray therapy there was a decrease in the size of the tumor mass in 17 patients, or

77 per cent, indicating a certain degree of radiosensitivity Judd and Larson reported that in 30 of 32 patients treated by x rays the tumors were radiosensitive. Newman and Pinck state that 4 patients with inoperable tumor were treated wholly by high voltage x ray Two of these failed to show improvement and 2 showed marked improvement as manifested by a decrease in the size of the tumor mass, relief of pain and a subjective feeling of well-being In our group of malignant tumors 41 received only x ray therapy

TABLE 105 END RESULTS OF X RAY THERAPY IN NONRESECTABLE RETROPERITONEAL TUMORS AT THE MEMORIAL HOSPITAL

Survival Period	*Total Cases*	*Dead*	*Lost to Follow-up*	*Living*
Total cases	42	34	7	1
1–12 mos.	25	21	4	0
13–24 mos	9	8	1	0
2–3 yrs.	2	2	0	0
3–5 yrs	2	1	1	0
Over 5 yrs.	4	2*	1†	1‡

* Patient with liposarcoma died from cancer over 6 years after treatment

Patient with Hodgkin s disease died from other causes, free of cancer 12 years after treatment

† Patient with lymphosarcoma lost to follow up free of cancer 13 years after treatment

‡ Patient with sarcoma of undetermined histogenesis living free of cancer 8 years after treatment

The results of treatment are not good except for the fact that patients had advanced inoperable cancers. The patients living over 5 years after completion of x ray therapy include one with liposarcoma who lived over 6 years before dying from his disease, one with Hodgkin s disease who lived 12 years and then died of other causes free of Hodgkin s disease and one with sarcoma of undetermined histogenesis who died from cancer 8 years later One patient with lymphosarcoma was lost to follow-up but was still free of evidence after 13 years two patients with benign fibromas treated by x ray therapy were still alive and well after 7 and 14 years, respectively although still showing evidence of residual tumor

2. Recurrent tumors following previous attempts at resections

3 Residual tumor left behind because of adherence to or infiltration of some vital organ. A very useful procedure in this regard is to mark the region and extent of the residual tumor at the time of operation with MacKenzie silver clips Roentgenograms of the abdomen in various planes postoperatively will permit irradiation to be directed much more accurately to the site of the residual tumor

4. Certain radiosensitive tumors are better treated by x rays than with surgery This applies particularly to the group of malignant retroperitoneal lymphomas, i.e giant follicular lymphosarcoma and Hodgkin s disease. These lesions are generally of multicentric origin (Treatment with surgery is restricted to those early cases of unicentric origin which are situated in more readily accessible regions such as the neck, groin, or axilla.)

5 Finally x ray therapy is recommended as an adjuvant to surgery for some malignant neoplasms such as the rhabdomyosarcoma (the embryonal variety in particular) neuroblastoma, and all other undifferentiated and anaplastic sarcomas. Wittenborg has indicated that in neuroblastoma his and his colleagues practice is to give postoperative irradiation as soon as possible after surgical treatment. The patients are brought directly from the operating room to the x ray therapy department and treatment is initiated on the day of operation They have found that immediate postoperative x ray therapy in children with air doses to the skin of 1400 r and 1800 r within 7 to 10 days, does

TABLE 106 END RESULTS OF TREATMENT OF MALIGNANT RETROPERITONEAL TUMORS AT THE MEMORIAL HOSPITAL

Histologic Type of Tumor	*No of Cases*	*No of Treatments*	*Laparotomy*		*Laparotomy and X-ray Therapy*				*Excision*			*Radical Excision*		
			Died With Cancer	*Lost Track of*	*Living Without Cancer*	*Living With Cancer*	*Died With Cancer*	*Lost Track of*	*Living Without Cancer*	*Living With Cancer*	*Died With Cancer*	*Living Without Cancer*	*Living With Cancer*	*Died With Cancer*
Total cases	103	4	9	1	1	4	47	8	1	2	3	10	4	9
Rhabdomyosarcoma	22	1	2	0	0	1	8	0	0	1	1	1	2	5
Liposarcoma	17	1	0	0	0	1	9	0	1	1	0	1	2	1
Leiomyosarcoma	5	0	0	0	0	1	0	1	0	0	0	2	0	1
Lymphosarcoma	18	0	3	0	0	1	11	1	0	0	1	1	0	0
Hodgkin's disease	6	0	1	0	0	0	5	0	0	0	0	0	0	0
Sarcoma of undetermined histogenesis	8	0	3	0	1	0	3	1	0	0	0	0	0	0
Carcinoma	7	0	0	1	0	0	4	2	0	0	0	0	0	0
Fibrosarcoma	6	1	0	0	0	0	2	3	0	0	0	0	0	0
Neuroblastoma	4	0	0	0	0	0	2	0	0	0	0	0	0	0
Ganglioneuroma	1	0	0	0	0	0	0	0	0	0	0	1	0	1
Mesothelioma	2	0	0	0	0	0	0	0	0	0	0	1	0	0
Myxoma	2	1	0	0	0	0	1	0	0	0	0	0	0	1
Malignant schwannoma	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Hemangiopericytoma	1	0	0	0	0	0	0	0	0	0	0	1	0	0
Synovial sarcoma	1	0	0	0	0	0	0	0	0	0	0	1	0	0
Chordoma	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Pheochromocytoma														
(extra-adrenal)	1	0	0	0	0	0	1	0	0	0	0	0	0	0
			0	0	0	0	0	0	0	0	0	1	0	0

ot result in wound breakdown The ame principle of treatment has been sed in the treatment of Wilms s tumor f the kidney at the Boston Childrens Hospital where the survival rate rose om 32 per cent with surgical excision alone to 47 per cent with surgery and postoperative irradiation. The more recent use of this combined form of therapy will undoubtedly effect improved future results in the management of many retroperitoneal tumors

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CHAPTER 29

Sarcoma of the Buttock

BY LEMUEL BOWDEN AND ROBERT J. BOOHER

Surgical management of malignant neoplasms is determined largely by the anatomic location of the tumor Although neoplasms may vary considerably in histologic appearance, generic type, metastasizing potentialities, and prognostic significance, they usually require the surgeon, in planning treatment, to categorize them in accordance with their anatomic location Although soft-part sarcomas of the buttocks may similarly vary in histology and behavior, a rational therapeutic approach requires that they be considered as an entity

RADICAL LOCAL RESECTION OF THE BUTTOCK

Undoubtedly such a procedure as hereinafter described has been previously performed intentionally or unwittingly by others Indeed, guidance by the previously published works of Stookey, of Henry, and of Aird, from whose operative technics the present surgical procedure is derived, is gratefully acknowledged

TECHNIC

After endothracheal anesthesia has been induced, the patient is placed in the prone position, the afflicted buttock and upper thigh surgically prepared, and the operative field so draped, by sterilely wrapping the entire leg, that the patient may subsequently be moved into the lateral decubitus position, should this be required, without grossly contaminating the operative field

A generous elliptical incision is made around the tumor down to the subcutaneous fat (Fig 462) The skin is dissected from fat by gentle retraction on the outer skin edge, and the incision is made down to the underlying gluteal fascia well under the skin flaps thus developed, so as to remove most of the subcutaneous fat with the specimen The origin of the gluteus maximus muscle from the lateral edge of the sacrum and coccyx and from the posterior portion of the iliac crest is thus exposed medially, and its largely aponeurotic insertion into the greater trochanter of the femur and into the iliotibial band exposed laterally A vertical incision is then made through the tendon of insertion of the gluteus maximus muscle beginning at the superior border of the muscle and extending downward and medially into the iliotibial tract to its posterior edge (Fig 463)

By upward and inward retraction of the transected gluteus maximus, the underlying piriformis muscle is readily visualized and the sciatic nerve emerging from the pelvis beneath its inferior

edge identified (Fig. 464) By inspection and palpation beneath the gluteus maximus at this point, it may be determined whether the neoplasm has been adequately cleared on its deep aspect. If so the resection need proceed no deeper. The inferior gluteal vessels are visualized emerging beneath the tendon of the piriformis muscle and are secured under direct vision. The specimen already well mobilized, is retracted laterally and is removed by division of the extensive fibers of origin of the gluteus maximus (Fig 465)

On the other hand, it may be found that the gluteus maximus after division near its insertion cannot be reflected medially owing to deeper extension of the tumor. The tendon of the piriformis muscle is then divided and incision is continued up into the gluteus medius close to its insertion into the femoral trochanter (see Fig 464) By exploring beneath these muscles it is again determined whether the deep aspect of the neoplasm has been cleared. If so resection of the growth is completed by division of the fibers of origin not only of the gluteus maximus but of the gluteus medius and piriformis as well.

A large operative defect is thus inevitable (Fig 466) The closure of this defect may be accomplished by skin alone, when primary closure of the skin is possible, or by a thicker skin and subcutaneous pedicle graft swung into the defect from the surrounding tissues.

This procedure is well tolerated by the patient, and convalescence is usually uncomplicated. In spite of the extensive sacrifice of muscles primarily concerned with locomotion there has been surprisingly little disability exhibited by our patients in regaining a walking gait or in maintaining erect posture.

Comment

It is quite apparent that the just-described operative procedure will not be

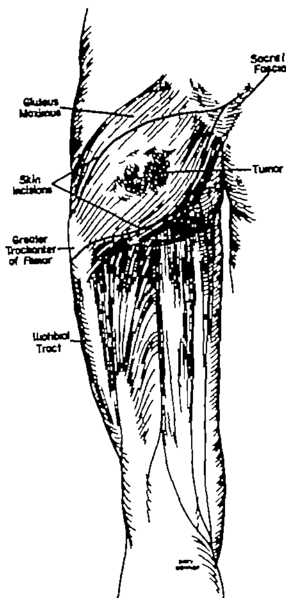


Fig. 462. Diagrammatic representation of sarcoma of the buttock, showing lines of skin incision for local resection of the tumor (*Courtesy* L. Bowden and R. J Booher and Cancer 6 89 1953)

applicable to all sarcomas of the buttock. Certain sarcomas may have extended to the underlying bony pelvis invading the periosteum or even the bone itself. A curative resection in such instances naturally requires sacrifice of the involved bone. Other sarcomas by downward extension into the thigh may have surrounded or invaded the sciatic nerve, occasionally protruding through the sciatic notch into the pelvic cavity. A curative resection of such a growth would require sacrifice of the sciatic nerve, leaving the patient with an essentially useless extremity

Determination of local operability of a tumor of the buttock is readily made early in the procedure when this technic is employed When the insertions of the gluteus maximus, gluteus medius, and piriformis muscles have been divided, neoplastic involvement of the iliac bone or of the sciatic nerve is recognizable at once, and further attempts at local resection may be forthwith abandoned

HEMIPELVECTOMY FOR SARCOMA OF THE BUTTOCK

Having determined local inoperability of a tumor of the buttock because of iliac-bone or sciatic-nerve involvement, hindquarter amputation still may offer the patient an opportunity for cure Hemipelvectomy may at once be undertaken (see Chap 12)

TECHNIC

The operative wound in the buttock is temporarily covered with moist sterile pads, the patient turned into the lateral decubitus position, and such additional sterile drapes applied as may be required The elliptical incision already made in the buttock is extended laterally over the greater trochanter of the femur well down into the anterior thigh, across the thigh, and then sharply up to the pubis, thus outlining a long anterior flap for subsequent closure The skin flap thus outlined is deepened through the entire thickness of subcutaneous fat and superficial and deep fascia This thick flap is then developed upward to expose the iliac crest and inguinal ligament (Fig 467)

In developing this long anterior skin flap, the femoral vessels are identified in the lower angle of the femoral triangle, they are here mobilized, ligated, and divided, and then proximal portion left attached to the overlying subcutaneous tissue by continuing the dissection deep to these vessels in the femoral triangle up to the point of their disappearance under the inguinal ligament The profunda femoris artery and certain branches of the circumflex femoral vessels must necessarily be ligated and divided in order to mobilize the superficial femoral vessels with the large skin flap, but the inferior epigastric vessels and other branches of the circumflex femoral and circumflex iliac vessels may be left intact to ensure adequate blood supply to the long anterior flap When this dissection has been completed the distal stump of the superficial femoral vein attached to the anterior flap should then be resected up to the point of entry of its first main branch This is obviously to lessen the possibility of subsequent thromboembolic complications that might result from stasis in this blind and functionless venous reservoir The inguinal ligament is severed medially from the pubic spine, and the rectus abdominis muscle divided at its intersection into the horizontal ramus of the pubis Laterally, an incision is made into the periosteum of the crest of the ilium, and by subperiosteal dissection the attachment of the inguinal ligament, together with the attachments of the external and internal oblique, the transversalis, and the quadratus lumborum muscles, are separated from the bony iliac crest (Fig 468) The iliac fossa is entered by gentle retraction upward and medially on the severed abdominal muscles and the extensive anterior flap thus developed

The periosteum is dissected free from the iliac fossa, the ureter identified and preserved, and the iliac vessels exposed Both the hypogastric artery and vein are ligated and divided at the bifurcation of the common iliac vessels, while the external iliac vessels are carefully retracted medially along with the peritoneum and abdominal contents in order to

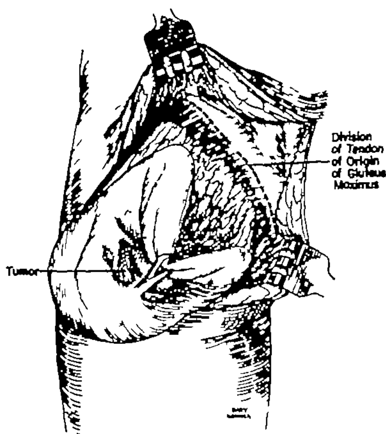


Fig. 465 The specimen, already largely mobilized, is retracted laterally and is removed by division of the tendinous origin of the gluteus maximus. (*Courtesy* L. Bowden and R. J Booher and *Cancer 6* 89 1953.)

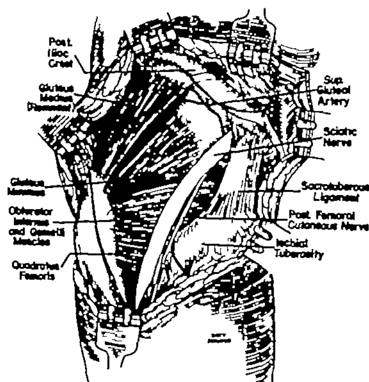


Fig. 466. Operative defect following radical resection of the buttock for sarcoma. (*Courtesy* L. Bowden and R. J Booher and *Cancer 6* 89 1953.)

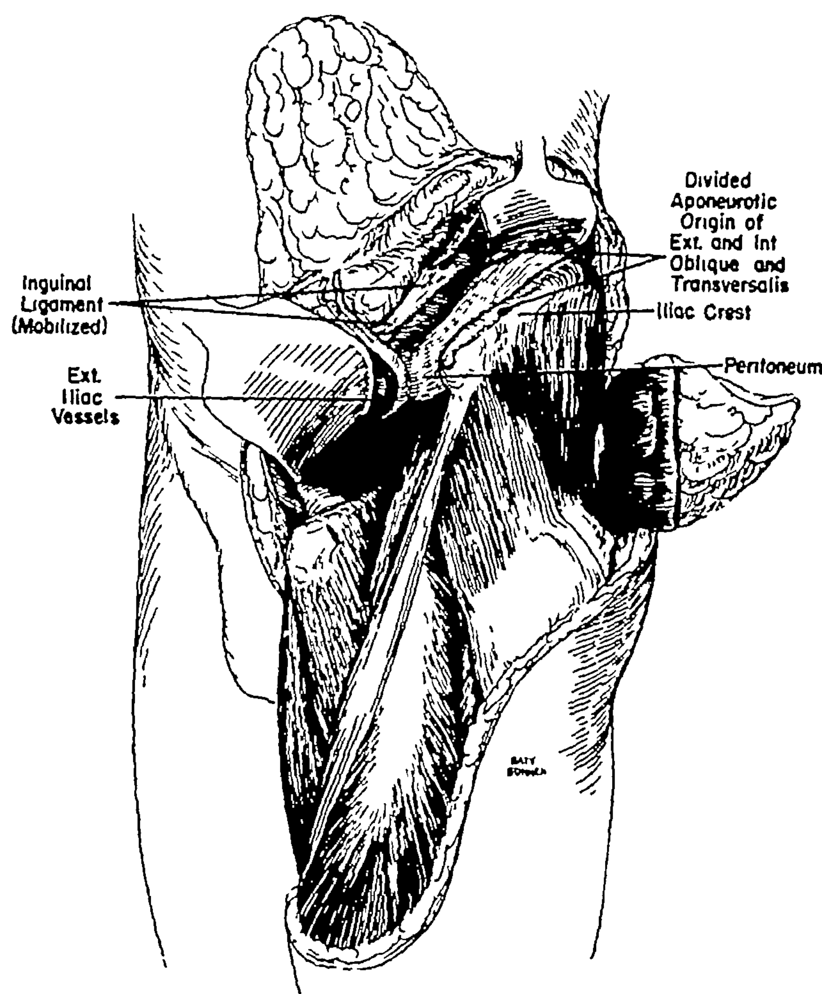


FIG 468 The lateral insertion of the inguinal ligament and the insertions of all the abdominal muscles arising from the iliac crest are divided by subperiosteal stripping of the entire iliac crest The iliac fossa is thus readily entered and widely exposed (*Courtesy,* L Bowden and R J Booher and Cancer *6* 89, 1953)

artery, on the contrary, is preserved for nutrition of the long anterior flap

The common iliac artery may be ligated in some instances without jeopardizing the viability of the skin flaps, but in order to lessen the likelihood of flap necrosis it is desirable to observe these anatomic considerations when technically feasible It has not been found necessary or advisable to occlude even temporarily the common iliac artery

Merendino has described a similar pedicle flap for covering large defects in the chest wall following interscapulothoracic amputation The bony thorax, however, presents no problem of postoperative hernia, which may be troublesome following hemipelvectomy In our cases of hemipelvectomy for sarcoma of the buttock, in which a well-vascularized, thick, anterior flap, including skin, subcutaneous fat, and deep fascia, was utilized, there was no tendency to postoperative hernia

The just-described surgical plan of treatment for sarcoma of the buttock has evolved over the past few years in proportion to the general interest in radical surgery for the cure of malignant tumors Hemipelvectomy, seemingly the most radical procedure possible in this anatomic area, in many instances may clear the tumor at the medial line of resection by a few millimeters of normal tissue only Local extirpation of the tumor may clear the tumor by a margin of normal tissue equally as wide Hence, it is obvious that local resection in this particular respect is as radical as hemipelvectomy

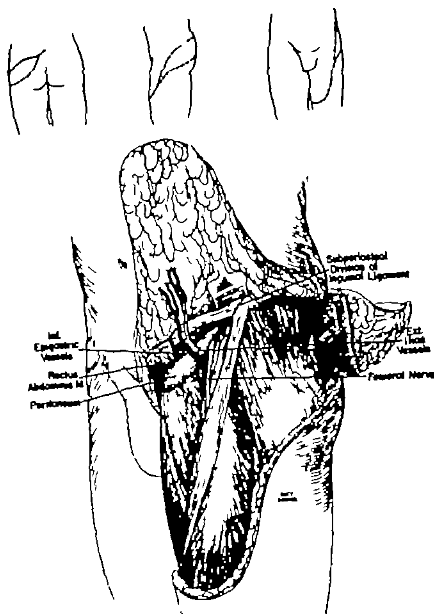


FIG. 467 Inserts demonstrate extension of primary buttock incision onto the thigh *to delineate a long anterior* skin flap for closure following hemipelvectomy The anterior flap is deepened through subcutaneous fat and superficial fascia and dissected up to the groin, including the superficial femoral vessels in the flap so developed. The inguinal ligament is divided at the pubic spine and the rectus abdominis muscle severed at its insertion into the pubic ramus. (*Courtesy* L. Bowden and R. J Booher and Cancer 6 89 1953)

preserve an adequate blood supply to the femoral vessels already preserved in the anterior flap Hemipelvectomy is from this point carried out in the standard manner

In the standard procedure for hemipelvectomy the skin and subcutaneous tissue of the entire buttock is preserved as a posterior flap for closure. In such instances the external iliac artery is ligated at its source and the hypogastric together with several of its branches is preserved for nutrition of the thick posterior flap In hemipelvectomy for sarcoma of the buttock, the entire buttock must necessarily be sacrificed. Ligation of the hypogastric artery at its origin is not only permissible but also is desirable in order to ablate the major blood supply to the tumor while the external iliac

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SECTION VI



Prognosis



TABLE 107 MALIGNANT TUMORS OF SOFT SOMATIC TISSUES OPERABILITY

Type of Case	Total Cases		Sarcoma of Undetermined Histogenesis		Liposarcoma		Rhabdomyosarcoma		Synovioma		Kaposi's Sarcoma		Malignant Neurilemmoma		Dermatofibrosarcoma Protuberans		Fibrosarcoma		Angiosarcoma	
	No	%	No	%	No	%	No	%	No.	%	No	%	No	%	No	%	No.	%	No	%
Total cases	717	100 0	261	100 0	105	100 0	100	100 0	60	100 0	48	100 0	46	100 0	39	100 0	39	100 0	19	100 0
Cases receiving definitive treatment	528	73 6	178	68 2	71	67 6	75	75 0	42	70 0	36	75 0	38	82 6	38	97 4	35	89 7	15	78 9
Primary operable	199	27 8	51	19 5	28	26 7	24	24 0	17	28 3	27	56 3	12	26 1	20	51 3	11	28 2	9	47 4
Recurrent operable	282	39 3	104	39 8	35	33 3	45	45 0	24	60 0	9	18 7	21	45 7	18	46 1	20	51 3	6	31 5
Postoperative x-ray	47	6 5	23	8 8	8	7 6	6	6 0	1	1 7	0	0 0	5	10 8	0	0 0	4	10 2	0	0 0
Cases receiving palliative treatment or none	189	26 4	83	31 8	34	32 4	25	25 0	18	30 0	12	25 0	8	17 4	1	2 6	4	10 2	4	21 1
Primary inoperable	35	4 9	11	4 2	9	8 6	7	7 0	1	1 7	3	6 3	4	8 7	0	0 0	0	0 0	0	0 0
Recurrent inoperable	91	12 7	44	16 8	19	18 1	7	7 0	9	15 0	2	4 1	2	4 3	0	0 0	4	10 2	4	21 1
Refused by patient	63	8 8	28	10 7	6	5 7	11	11 0	8	13 3	7	14 6	2	4 3	1	2 6	0	0 0	0	0 0

CHAPTER 30

End Results in the Treatment of Sarcomas of the Soft Somatic Tissues

To present the end results of treatment, certain graphic forms have been chosen in order to show clearly what can be accomplished for each histogenetic type. The indeterminate group of cases include those patients who refused the treatment advised, who did not complete the treatment, or who were treated elsewhere. Of the determinate cases those treated within the past five years cannot be used for analysis of cure rates. The balance of cases, treated more than five years ago constitute the material on which the definitive five-year-cure rates are based.

TABLE 109 RADICAL SURGERY FOR TUMORS OF THE SOFT SOMATIC TISSUES END RESULTS ACCORDING TO TYPE OF OPERATION

Histologic Type	*Total Cases*	*Indeterminate Cases*	*Cases Treated until Recently*	*Cases Treated over 5 Years Ago*	*Five-year Cures*	
					Number	*Percentage*
1. AMPUTATION						
Total cases	68	10	9	49	11	22 4
Malignant neurilemmoma	18	4	2	12	5	41 7
Liposarcoma	3	—	1	2	—	—
Rhabdomyosarcoma	8	2	—	6	1	16 7
Sarcoma, unclassified	7	1	1	5	—	—
Synovioma	17	—	2	15	2	13 3
Kaposi's sarcoma	6	3	—	3	—	—
Myxosarcoma	3	—	1	2	1	50 0
Fibrosarcoma	4	—	1	3	2	66 7
Angiosarcoma	2	—	1	1	—	—
2 INTERSCAPULOTHORACIC AMPUTATION						
Total cases	23	—	10	13	4	30 8
Malignant neurilemmoma	5	—	—	5	3	60 0
Rhabdomyosarcoma	5	—	1	4	1	25 0
Sarcoma, unclassified	4	—	2	2	—	—
Synovioma	5	—	3	2	—	—
Fibrosarcoma	2	—	2	—	—	—
Angiosarcoma	2	—	2	—	—	—
3 HIP-JOINT DISARTICULATION						
Total cases	24	1	11	12	2	16 7
Malignant neurilemmoma	3	—	1	2	2	100 0
Liposarcoma	3	1	—	2	—	—
Rhabdomyosarcoma	2	—	1	1	—	—
Sarcoma, unclassified	14	—	9	5	—	—
Synovioma	2	—	—	2	—	—
4 HEMIPELVECTOMY						
Total cases	10	—	9	1	—	—
Malignant neurilemmoma	1	—	—	1	—	—
Liposarcoma	3	—	3	—	—	—
Rhabdomyosarcoma	2	—	2	—	—	—
Sarcoma, unclassified	3	—	3	—	—	—
Kaposi's sarcoma	1	—	1	—	—	—
5 GROIN AND AXILLARY DISSECTIONS						
Total cases	17	1	3	13	6	16 2
Groin dissections	14	1	3	10	5	50 0
Liposarcoma	3	1	—	2	2	100 0
Rhabdomyosarcoma	6	—	1	5	2	10 0
Sarcoma, unclassified	1	—	—	1	1	100 0
Synovioma	4	—	2	2	—	—
Axillary dissections	3	—	—	3	1	33 3
Liposarcoma	2	—	—	2	—	—
Rhabdomyosarcoma	1	—	—	1	1	100 0

TABLE 108 RADICAL SURGERY FOR TUMORS OF THE SOFT SOMATIC TISSUES: END RESULTS ACCORDING TO HISTOLOGIC TYPE OF TUMOR

Type of Operation	*Total Cases*	*Indeterminate Cases*	*Cases Treated until Recently*	*Cases Treated Over 5 Years Ago*	*Five year Cures*	
					Number	*Percentage*
1 MALIGNANT NEURILEMMOMA						
Total cases	27	4	3	20	10	50 0
Amputation	18	4	2	12	5	41 7
Hip-joint disarticulation	3	—	1	2	2	100 0
Hemipelvectomy	1	—	—	1	—	—
Interscapulothoracic amputation	5	—	—	5	3	60 0
2 RHABDOMYOSARCOMA						
Total cases	24	2	5	17	5	29 4
Amputation	8	2	—	6	1	16 7
Hip-joint disarticulation	2	—	1	1	—	—
Hemipelvectomy	2	—	2	—	—	—
Groin dissection	6	—	1	5	2	40 0
Interscapulothoracic amputation	5	—	1	4	1	25 0
Axillary dissection	1	—	—	1	1	100 0
3 SARCOMA, UNCLASSIFIED						
Total cases	29	1	15	13	1	7 7
Amputation	7	1	1	5	—	—
Hip-joint disarticulation	14	—	9	5	—	—
Hemipelvectomy	3	—	3	—	—	—
Interscapulothoracic amputation	4	—	2	2	—	—
Groin dissection	1	—	—	1	1	100 0
4 SYNOVIOMA						
Total cases	28	—	7	21	2	9 5
Amputation	17	—	2	15	2	13 3
Hip-joint disarticulation	2	—	—	2	—	—
Interscapulothoracic amputation	5	—	3	2	—	—
Groin dissection	4	—	2	2	—	—
5 LIPOSARCOMA						
Total cases	14	2	4	8	2	25 0
Amputation	3	—	1	2	—	—
Hip-joint disarticulation	3	1	—	2	—	—
Hemipelvectomy	3	—	3	—	—	—
Groin dissection	3	1	—	2	2	100 0
Axillary dissection	2	—	—	2	—	—
6 KAPOSI'S SARCOMA						
Total cases	7	3	1	3	—	—
Amputation	6	3	—	3	—	—
Hemipelvectomy	1	—	1	—	—	—
7 MYXOSARCOMA						
Total cases	3	—	1	2	1	50 0
Amputation	3	—	1	2	1	50 0

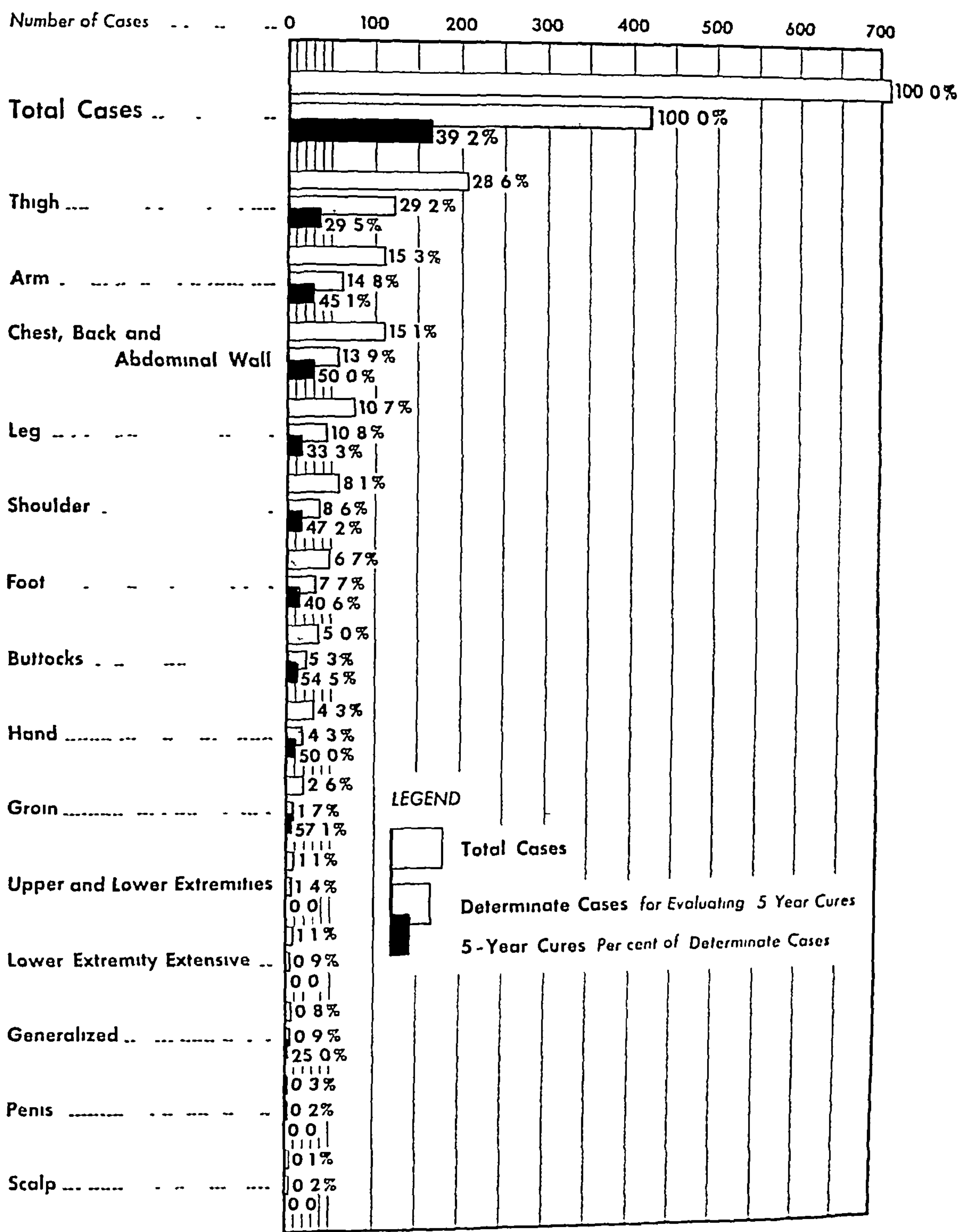


CHART 2

(G T Pack J Bone & Joint Surg 36- I 246–259, 1954 Courtesy, The Journal of Bone and Joint Surgery)

MALIGNANT TUMORS OF SOFT SOMATIC TISSUES

DISTRIBUTION ACCORDING TO HISTOLOGICAL TYPE

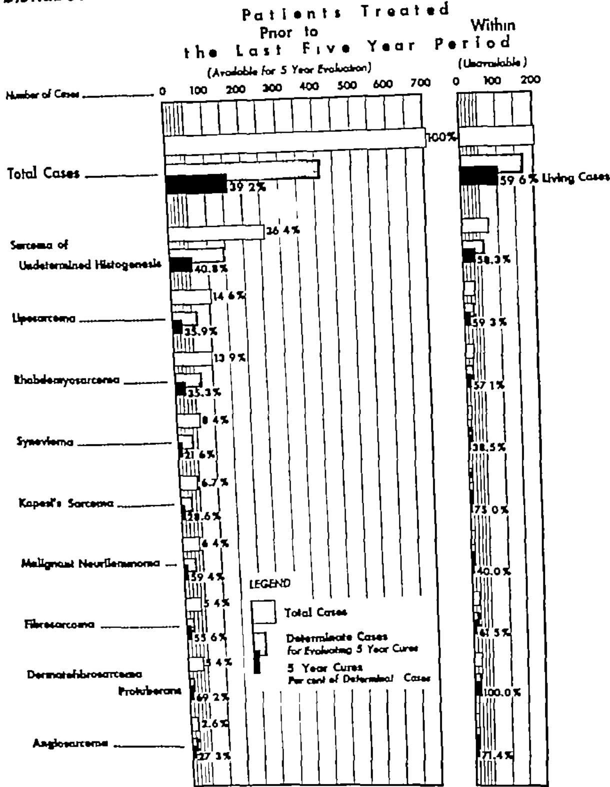


CHART 1

(G T Pack J Bone & Joint Surg 36-A 246-259 1954 Courtesy The Journal of Bone and Joint Surgery)

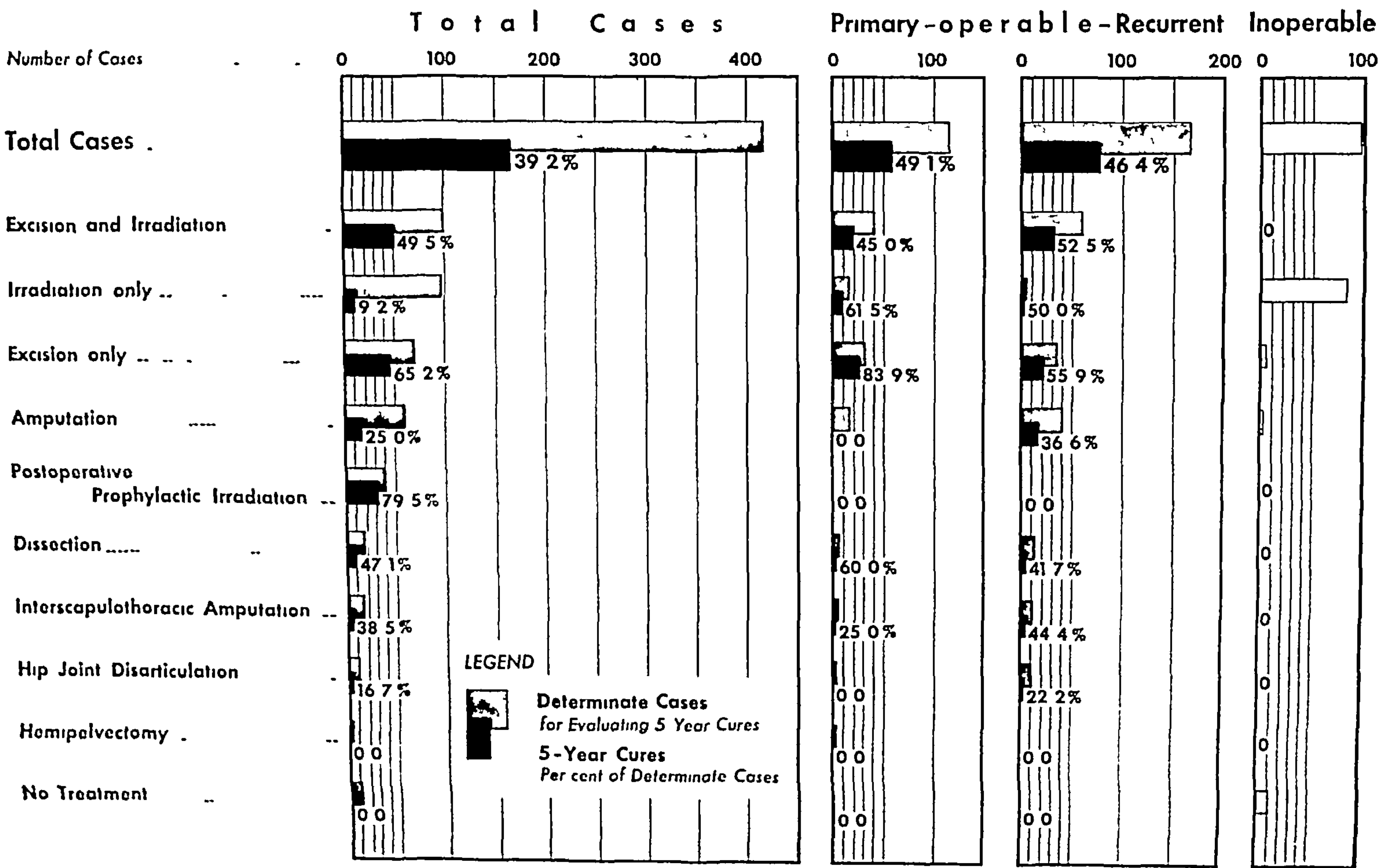


CHART 4

(G T Pack J Bone & Joint Surg 36-A 246–259, 1954 *Courtesy*, The Journal of Bone and Joint Surgery)

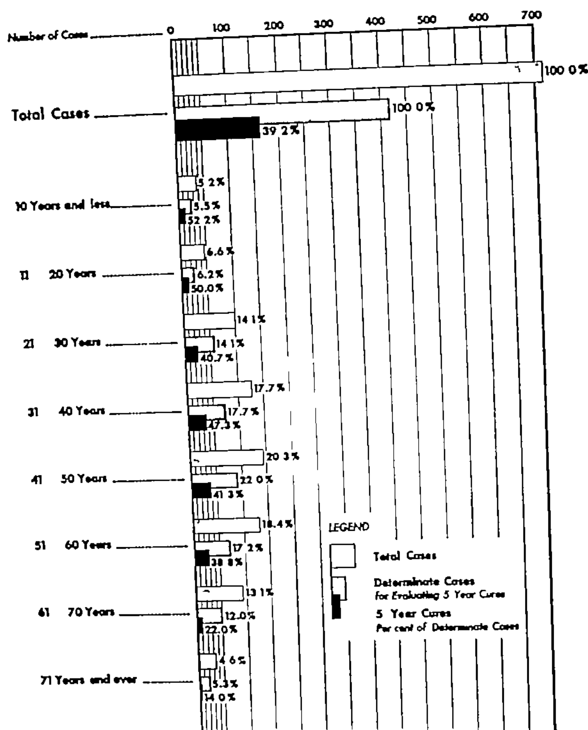


CHART 3

(G T Pack J Bone & Joint Surg 36-A:246-259 1954 Courtesy The Journal of Bone and Joint Surgery)

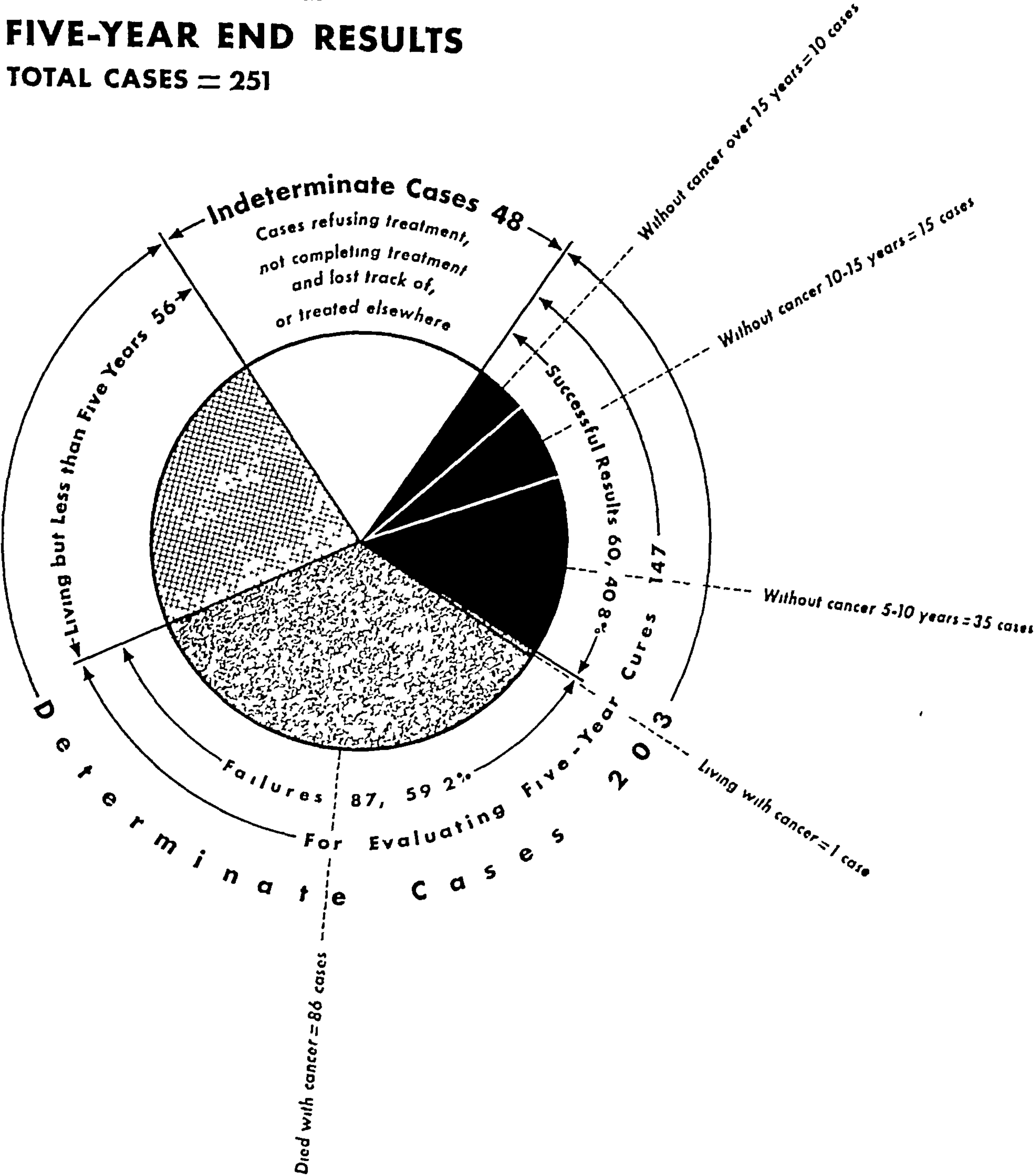


CHART 6

(G T Pack J Bone & Joint Surg 36-1 246–259, 1954 *Courtesy*, The Journal of Bone and Joint Surgery)

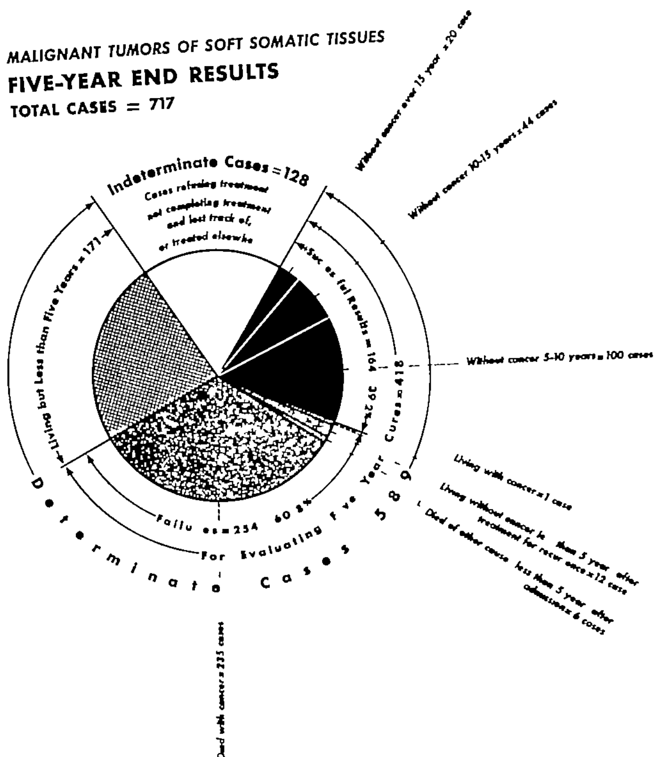


CHART 5
(G T Pack J Bone & Joint Surg. 36-A 46-259 1954 Courtesy The Journal of Bone and Joint Surgery)

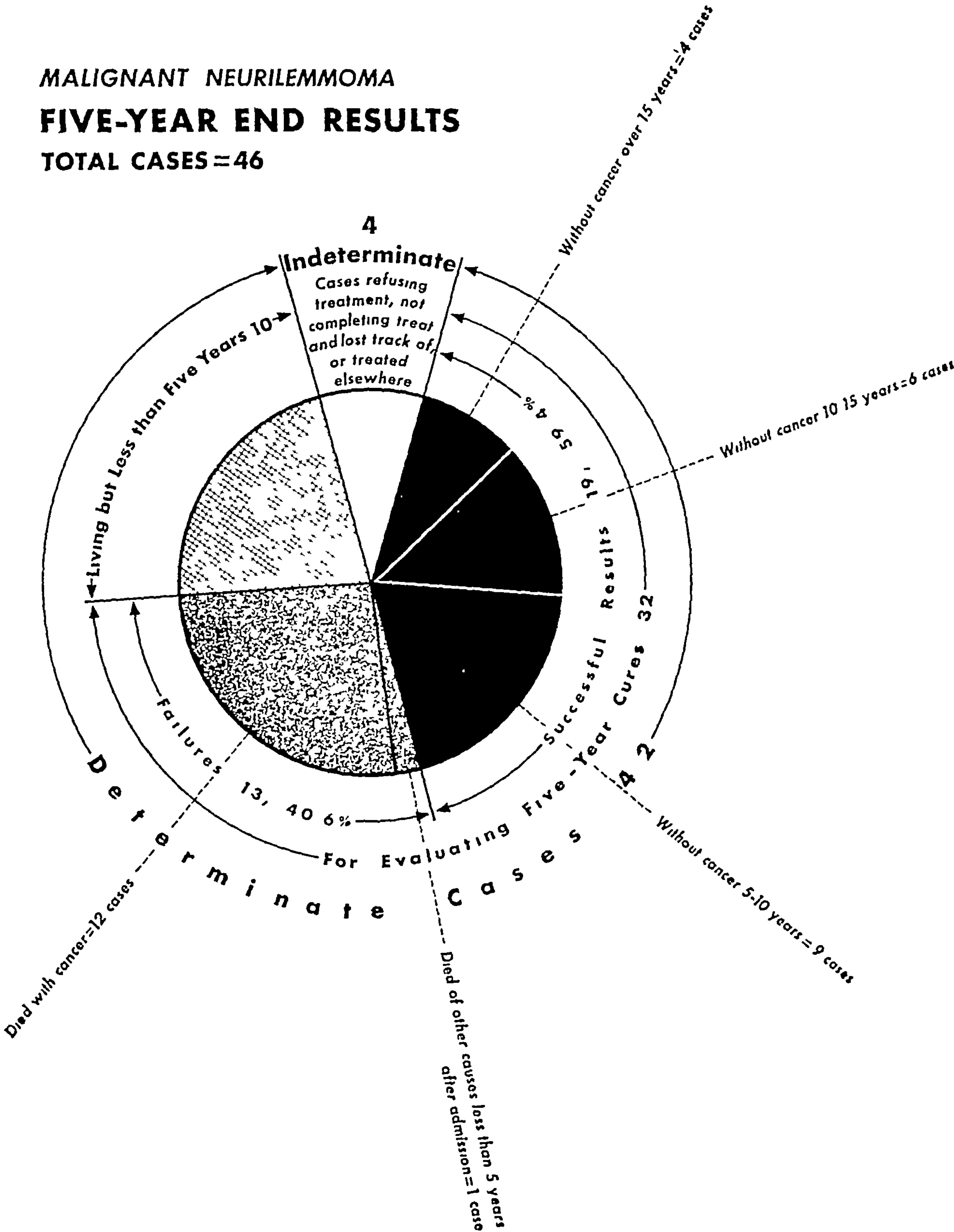


CHART 10

(G T Pack J Bone & Joint Surg 36-A 246-259, 1954 Courtesy, The Journal of Bone and Joint Surgery)

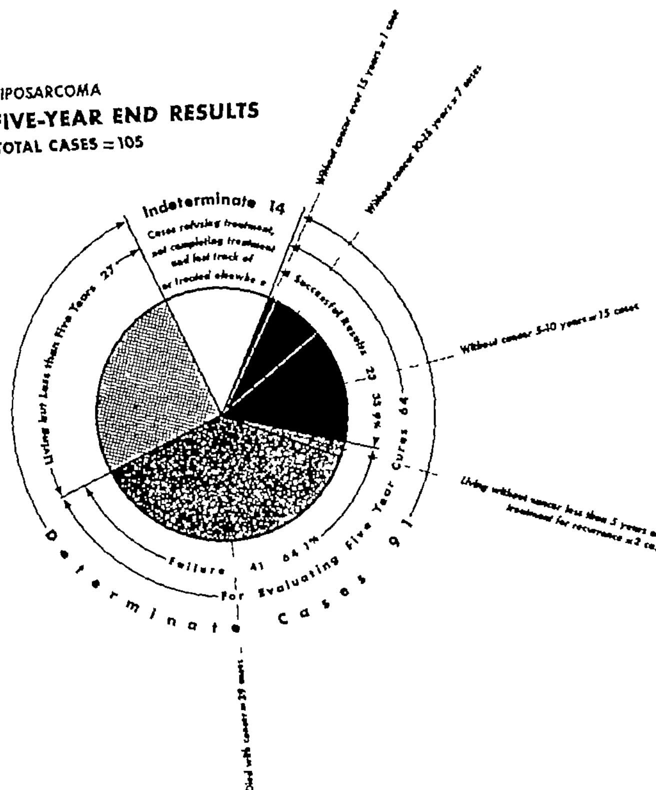


CHART 7
(G T Pack J Bone & Joint Surg. 36-A 46-255, 1954 Courtesy The Journal of Bone and Joint Surgery)

DERMATOFIBROSARCOMA PROTUBERANS

FIVE-YEAR END RESULTS

TOTAL CASES = 39

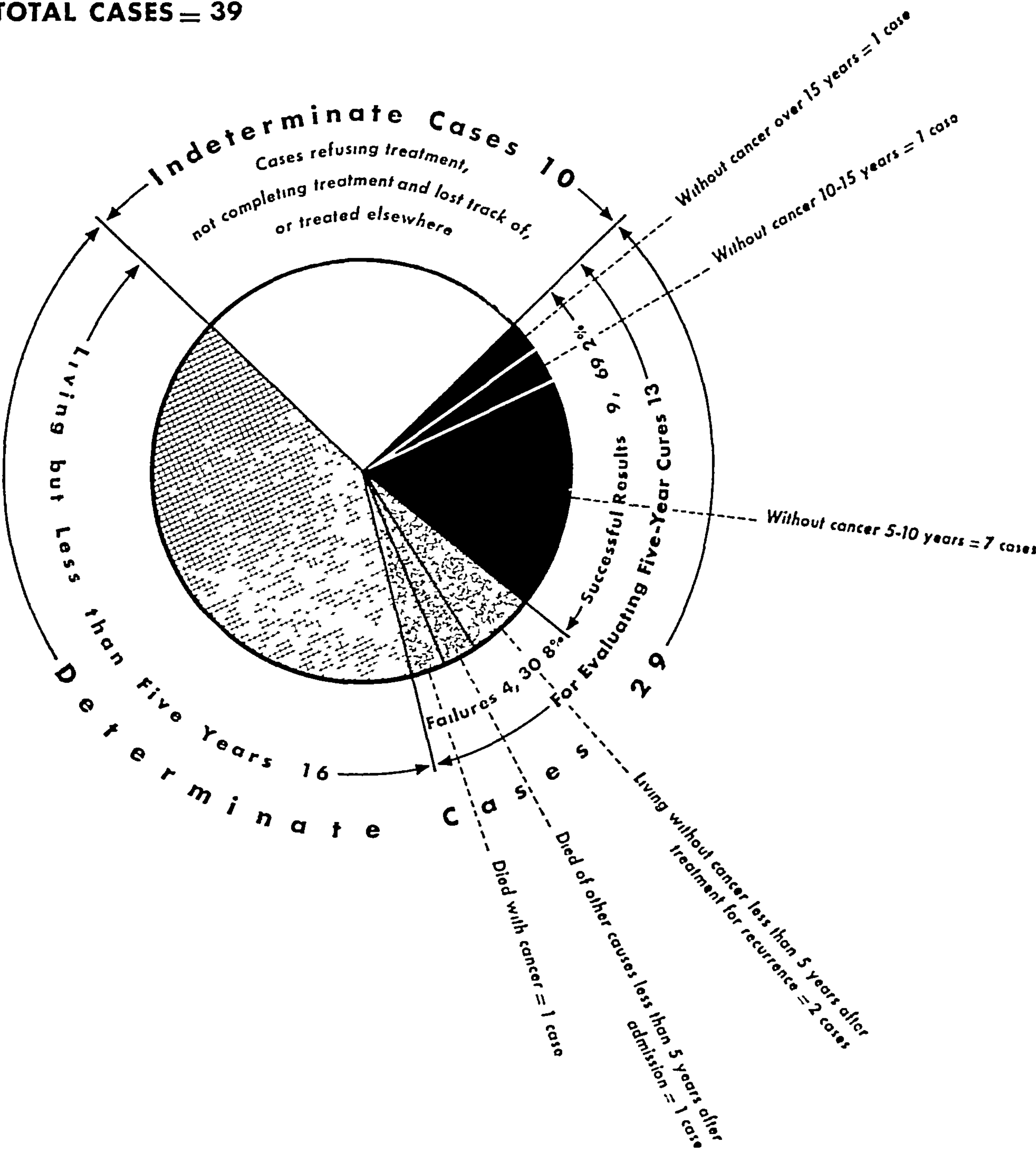


Chart 12

(G T Pack J Bone & Joint Surg 36-A 246–259, 1954 *Courtesy*, The Journal of Bone and Joint Surgery.)

FIBROSARCOMA

FIVE-YEAR END RESULTS

TOTAL CASES = 39

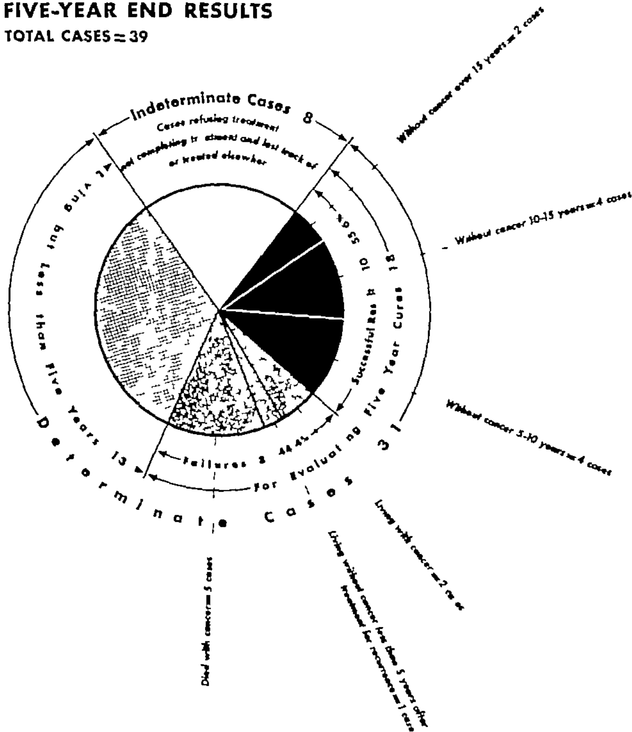


CHART 11

(G T Pack J Bone & Joint Surg. 36-A 246-259 1954 Courtesy The Journal of Bone and Joint Surgery)

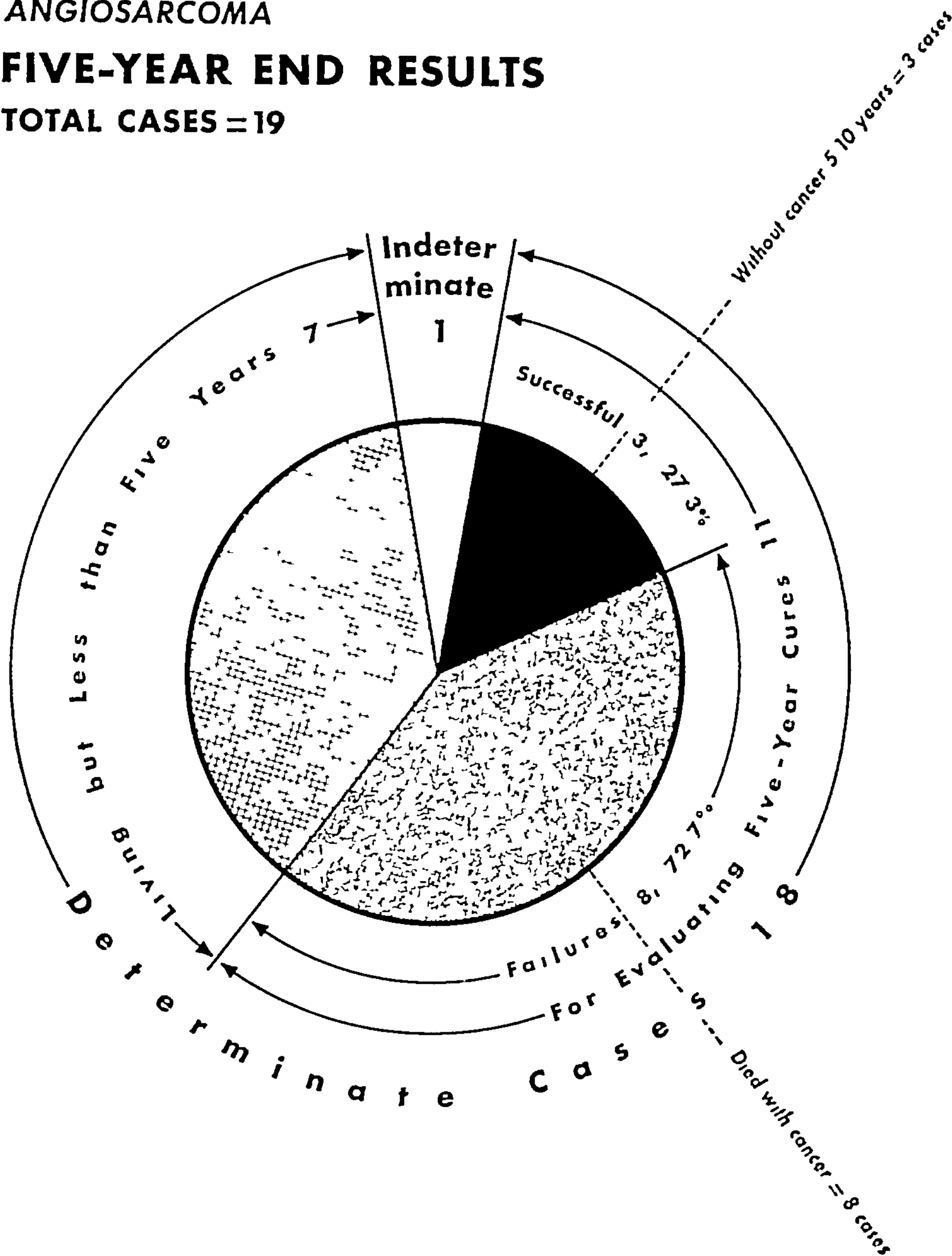


CHART 14

(G. T. Pack. J. Bone & Joint Surg. 36-A 246–259, 1954. *Courtesy*, The Journal of Bone and Joint Surgery.)

KAPOSI'S SARCOMA

FIVE-YEAR END RESULTS

TOTAL CASES = 48

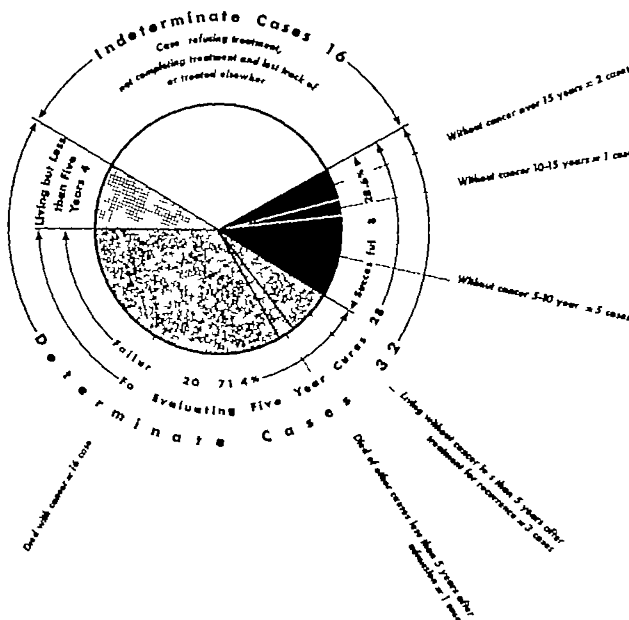


CHART 13

(G T Pack J Bone & Joint Surg 36-A 46-259 1954 Courtesy The Journal of Bone and Joint Surgery)

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The clinician who has treated patients and followed them for many years thereby acquires a fund of information concerning the natural history of a tumor and its response to treatment which, when taken together with the local setting of the cancer and its histologic classification, offers the proper basis for a decision concerning therapy.

As this is the first book on the subject to contain extensive data on the clinical features of these tumors and the results of therapy, we have attempted to make the book all-embracing, discussing the various disciplines that contribute to the cure of the patient The text is divided into six sections. Section I is devoted to a consideration of the natural history of tumors of the soft somatic tissues, their classification, incidence, hereditary and congenital occurrence, the roles played by trauma and other etiologic factors in their production, the question of malignant degeneration of benign somatic tumors, et cetera Section II discusses the technics of wide local excision, resection of the tumor and its lymph-node metastasis as a monobloc dissection, and the various types of amputations In Section III are described at length the different tumors which comprise this neoplastic group, as well as certain tumor-like or preneoplastic proliferations Section IV discusses sarcomas of infants and children and points out the good results that can be obtained in the treatment of these neoplasms of childhood Section V describes the principles of treating these neoplasms when they occur in certain anatomic locations such as the neck, the abdominal wall, the buttocks, and the retroperitoneum. Section VI is an over-all summary of the end results of treatment of malignant tumors of the soft tissues, with a critical analysis to evaluate those factors that influence prognosis

The text is accompanied by 109 tables and more than 600 illustrations Representative bibliographies at the ends of the chapters provide guidance for those who may seek further information and indicate the works of authors referred to in the text

We recognize many hiatuses in knowledge pertaining to this cancer group—for example, the inability to classify some soft part sarcomas according to their cells of origin, and the reason why certain apparently benign neoplasms may after many years generate growth momentum and become clinically malignant

We confess to a strong interest in this subject and have attempted to present in a concise and readable manner this complex branch of oncology. We hope thereby to contribute toward a better understanding of this form of cancer and to a lowered mortality therefrom

G. T. P

I M A

New York

Preface

This book describes in detail the clinical management of patients bearing tumors of the soft somatic tissues. It is based on the results of twenty-five years of study of the clinical behavior of such tumors. The soft somatic tissues, comprising the organs of locomotion, support, and lubrication and consisting of connective tissue, fat, smooth and striated muscle, fascia, synovial structures, blood and lymph vessels, and nerve tissue, give rise to a large and varied group of neoplasms. The book explains step-by-step how each type of tumor should be handled, from the initial clinical evaluation of the patient to the performance of the biopsy and the institution of the therapeutic plan, and discusses the anticipated prognosis. Each tumor type is analyzed, and criteria are presented for differentiating benign tumors and tumorlike growths from malignant neoplasms arising from the structures under discussion.

The monograph offers an evaluation of the results of treatment of the largest number of neoplasms of the soft somatic tissues ever reported from a single source. The patients in this report have come, in the main, from the Mixed Tumor Service of the Memorial Center for Cancer and Allied Diseases and the Pack Medical Group. Perhaps its greatest value lies in the fact that all were diagnosed and treated by a single group, with treatment policies being subjected to group judgment.

A quarter of a century has afforded adequate time for critical judgment of the effects of different methods of treating sarcomas and to evolve forms of therapy that by statistical analysis have proved to be best for a given patient with a given histologic type of sarcoma in a given anatomic location. Treatment methods have been retained or abandoned, depending upon their respective successes or failures.

A gratifying observation resulting from an analysis of these cases is the definitive curability. The over-all five-year survival rate without recurrence of sarcomas of the soft somatic tissues is 39 per cent.

In our opinion, the choice of treatment should not rest on the pathologist's report alone. Rather, proper therapy depends not only on the histologic criteria but, more importantly, upon the location of the tumor, the extent of its invasion, its mobility, its fixation or adherence to joint capsules, and many other factors that only clinical examination can ascertain. We have found these clinical factors of greater importance, for example, in making the choice between radical local dissection and amputation than is the correct diagnosis of the histogenesis of the sarcoma in question.

The clinician who has treated patients and followed them for many years thereby acquires a fund of information concerning the natural history of a tumor and its response to treatment which, when taken together with the local setting of the cancer and its histologic classification, offers the proper basis for a decision concerning therapy

As this is the first book on the subject to contain extensive data on the clinical features of these tumors and the results of therapy, we have attempted to make the book all-embracing, discussing the various disciplines that contribute to the cure of the patient. The text is divided into six sections Section I is devoted to a consideration of the natural history of tumors of the soft somatic tissues, their classification, incidence, hereditary and congenital occurrence, the roles played by trauma and other etiologic factors in their production, the question of malignant degeneration of benign somatic tumors, et cetera Section II discusses the technics of wide local excision, resection of the tumor and its lymph-node metastasis as a monobloc dissection, and the various types of amputations In Section III are described at length the different tumors which comprise this neoplastic group, as well as certain tumorlike or preneoplastic proliferations Section IV discusses sarcomas of infants and children and points out the good results that can be obtained in the treatment of these neoplasms of childhood. Section V describes the principles of treating these neoplasms when they occur in certain anatomic locations such as the neck, the abdominal wall, the buttocks, and the retroperitoneum Section VI is an over-all summary of the end results of treatment of malignant tumors of the soft tissues, with a critical analysis to evaluate those factors that influence prognosis

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We confess to a strong interest in this subject and have attempted to present in a concise and readable manner this complex branch of oncology. We hope thereby to contribute toward a better understanding of this form of cancer and to a lowered mortality therefrom

C T. P
I M A

New York

"fibrous tissue" He also reported the case of Freudenstein of a 12 year-old boy with a fibromatous tumor of six months duration that was derived from the superficial fascia of the abdomen. The single case of Pfeiffer's series, in a girl of 2½ years was present at birth, the lesion arose in the superficial abdominal fascia and grossly resembled a fibroma, although no histologic diagnosis was given.

Jemma's own case is well documented. The girl, aged 3½ years, for three years had a progressively enlarging nodule in the right lower abdominal quadrant. The excised tumor weighed 650 gm.

Grenet and Mezard in 1931 recorded the case of a 2-year-old girl whose tumor the size of a hen's egg, was only "recently noticed." It weighed 65 gm. and was reported as a "pure fibroma without any sarcomatous cells" These authors also report, though not in detail two female patients of Kramer one 2 and the other 4½ years old.

In 1934 Walters and Church reviewed 44 desmomas of the abdominal wall at the Mayo Clinic and listed their youngest patient as 2 years old Geschickter and Lewis in 1936 reported a girl of 12 years as their youngest patient.

Waugh in 1940 reported in some detail the case of a 5-year-old boy who one and a half years before admission had fallen off a bed, injuring the right upper abdomen One month after the injury the child's doctor had noted a small tumor and within four months time it measured 7 × 10 cm. It was at first considered to be an unresolved hematoma but excision revealed it to be a desmoid tumor adherent to an anterior costochondral junction The author summarized his view that in many instances desmoid tumors apparently arise secondary to trauma and their pathogenesis is probably related to a disturbance in the organization of the ensuing hematoma, a theory going back to Paget.

Ladd and Gross have shown a photograph of a 21 month-old girl with a central subumbilical lesion which they report as a perineural fibroblastoma They state that "some pathologists believe that desmoid tumors are perineural fibroblastomas, and the histology in one of our specimens strongly suggested such an origin in spite of the fact that the mass seemed to arise from the anterior rectus fascia." This is the only known report of this lesion referred to as a schwannoma, which makes it difficult, without any histologic background afforded, to accept this case as a true desmoid tumor

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in considerable loss of fascial and muscular structures of the anterior abdominal wall, the patients require considerable postoperative bed rest. It has been our policy to keep the lower limbs flexed by means of pillows, bed adjustment, or an overhead knee sling so that the broad abdominal muscles remain continually relaxed during the period of healing. Daily enemas and prompt treatment of cough are necessary measures in the aftercare.

Patients should be warned against subsequent pregnancies because of the high incidence of recurrences following childbirth.

Radiation Therapy

According to Ewing, the majority of these tumors respond slowly but satisfactorily to irradiation. This statement apparently has not been generally accepted, for most reports on desmoid tumors either mention no experience with roentgen therapy for this neoplasm or state that the growth did not respond to irradiation (Mason, Mankin, and Pearman and Mayo). In the present series there were three inoperable cases which were satisfactorily controlled with high-voltage roentgen or radium-element pack therapy. Almost all recurrences were treated successfully with high-voltage roentgen ray therapy. The only recurrence which was treated unsuccessfully with irradiation was in a male patient. Many of our patients received preoperative roentgen or radium-element pack therapy.

It is difficult to understand why such a large proportion of desmoid tumors should respond to high-voltage radiation therapy. There is nothing in the histologic structure of the neoplasm to suggest radiosensitivity. Muscle-infiltrating fibromas and nonmetastasizing fibrosarcomas of the fascia-tendon type in locations other than the anterior abdominal wall either cannot be controlled by large doses of irradiation or respond feebly and inadequately to such treatment. This suggests, then, that the response of desmoid tumors to irradiation may be an indirect one, i.e., due to suppression or cessation of ovarian function (radiation castration). Such a hormonal hypothesis may also explain why a small dose (from 1000 to 1500 r) directed to the tumor site does not retard the growth and why larger doses (of at least 5000 r and the portal to include the entire lower abdomen) are necessary to effect complete regression or satisfactory control of the tumor. The radio-resistance of the neoplasm in males supports this hypothesis.

Radiation therapy has a definite place in the management of desmoid tumors but is not to be preferred to primary radical surgical excision, which is the treatment of choice. Radiation therapy should be reserved for inoperable cases, large tumors in poor-risk patients, and for those who will not consent to operation. Irradiation is not a satisfactory therapeutic agent in the treatment of desmoid tumors in male patients.

PROGNOSIS AND END RESULTS

Although desmoid tumors may undergo complete malignant transformation, no instance was encountered, either in this series or in cases previously reported, in which there were regional lymph node or distant metastases. However, these tumors may occasionally become sufficiently aggressive to invade the abdominal and pelvic cavities and to produce an inoperable and hopeless situation. If treatment is delayed or inadequate, the neoplasm may reach huge proportions, actually replacing the anterior abdominal wall, or it may become adherent to the periosteum of adjacent bones or infiltrate into the sacroiliac joints, so as to make complete surgical removal hazardous or impossible. If dissection of the tumor and the surrounding structures is not radical and thorough

Case Number	Sex and Age	Duration of Tumor	Size of Tumor	Number of Pregnancies	Number of Childbirths	Postpartum Interval before Appearance of Tumor	Muscles Involved	Topographical Distribution	Osseous Attachment	Peritoneal Involvement	Recurrences Prior to Admission	Recurrences after Excision at Memorial Hospital	Recurrences Following Pregnancy	Malignant Transformation	Response to Irradiation (Recurrences)	Follow-up Period (Yr)	End Results
9 M D	F 31	9 mo	5 cm.	1	1	6 mo	Rectus abdominis	Left lower abdominal quadrant	0	0	0	0	0	0	—	8	Cured
10 M F	F 22	1 yr	6 cm.	1	1	3 yr	Rectus abdominis	Left lower abdominal quadrant	0	0	1	1	0	0	+	7	Cured
11 G M	F 30	5 mo	4 cm	1	1	1 yr	External oblique	Right lower abdominal quadrant	+	0	0	0	0	0	—	5	Cured
12 T R.	F 26	9 yr	20 cm	0	0		?	Right upper and lower quadrants and left lower quadrant	+	+	0	—	—	0	±	5	Controlled
13 M A.	F 23	2 yr	10 cm.	1	1	During gestation	Rectus abdominis	Right lower abdominal quadrant	0	+	1	0	0	0	—	4	Cured
14 L. K.	M 64	2 yr	7 cm.				Rectus abdominis	Right lower abdominal quadrant	0	0	0	0		+	—	3	Cured
15 D R.	F 25	6 mo	5 cm	2	2	1 mo	Rectus abdominis	Left paraumbilical region	0	0	0	0	0	0	—	2	Cured
16 E S	F 31	1 yr	8 cm.	2	2	3 mo	Rectus abdominis	Left lower abdominal quadrant	+	+	1	0	+	0	—	1	Cured
17 F B	F 24	8 mo	4.5 cm	2	2	2 mo	External oblique	Left lower abdominal quadrant	+	0	0	0	0	0	—	½	Cured

"fibrous tissue." He also reported the case of Freudenstein of a 12-year-old boy with a fibromatous tumor of six months' duration that was derived from the superficial fascia of the abdomen The single case of Pfeiffer's series, in a girl of 2½ years, was present at birth, the lesion arose in the superficial abdominal fascia and grossly resembled a fibroma, although no histologic diagnosis was given

Jemma's own case is well documented The girl, aged 3½ years, for three years had a progressively enlarging nodule in the right lower abdominal quadrant The excised tumor weighed 650 gm

Grenet and Mezard in 1931 recorded the case of a 2-year-old girl whose tumor, the size of a hen's egg, was only "recently noticed" It weighed 65 gm and was reported as a "pure fibroma without any sarcomatous cells" These authors also report, though not in detail, two female patients of Kramer, one 2 and the other 4½ years old

In 1934 Walters and Church reviewed 44 desmomas of the abdominal wall at the Mayo Clinic and listed their youngest patient as 2 years old Geschickter and Lewis in 1936 reported a girl of 12 years as their youngest patient

Waugh in 1940 reported in some detail the case of a 5-year-old boy who one and a half years before admission had fallen off a bed, injuring the right upper abdomen One month after the injury the child's doctor had noted a small tumor and within four months' time it measured 7 × 10 cm It was at first considered to be an unresolved hematoma, but excision revealed it to be a desmoid tumor adherent to an anterior costochondral junction The author summarized his view that in many instances desmoid tumors apparently arise secondary to trauma and their pathogenesis is probably related to a disturbance in the organization of the ensuing hematoma, a theory going back to Paget

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recurrences are the rule. The tumor may recur in spite of adequate surgical excision unless a sufficient amount of preoperative or postoperative radiation has been delivered to the tumor site and its surrounding tissues (except in males) Recurrences are common during and following subsequent pregnancies

In this series there were four patients in whom the tumor recurred and one case in which there were two recurrences All recurrences responded satisfactorily to radiation therapy except in one instance in which the patient failed to appear for follow up examinations until the tumor had invaded the peritoneal cavity and in one male patient in whom surgical excision was resorted to after an apparently adequate course of irradiation failed to control the tumor

DESMOMAS OF THE ABDOMINAL WALL IN CHILDREN*

Historic Review

Temoin in 1893 was the first author to describe a desmoid tumor of the abdominal wall in a child. His case is of great interest because the patient's mother first noted that her child, when 2 years old, had a hard mobile tumor of the abdominal wall the size of a walnut it grew within a year to the size of a fist. When he operated on the girl, when she was 14 the tumor was the size of a child's head, extending from the false ribs to the crural arch and overhanging the upper one-third of the thigh. He described Bouchacourt's sign as present. The gross description of a tumor of 1400 gm "resting deeply" in the peritoneum coincides with a desmoid tumor and it is reported as such but the histologic examination is described as a "fibrolipomatous tumor" There was no evidence of recurrence after two and a half years.

It was Greig, in 1915 who first reported the occurrence of a desmoid tumor in the sheath of the rectus abdominis muscle in a female child aged 20 months It was first noted at 8 months He considered a congenital origin quoting Pfeiffer's opinion that "a rare case or two considered congenital is on record. In my case I have no doubt the tumor was a congenital one for it was of considerable size when it was noticed at the age of 8 months, and it had grown slowly if at all, after that " In his consideration of the cases reported to that time, he made two generalizations one was the "difficulty of separating what might be true desmoids from fibro-sarcomata and typical sarcomata" and "the great rarity with which desmoids have been observed in infants"

In Greig's case the characteristic features are typical and indicate that the desmoid tumor of childhood is little different from its adult prototype, the tumors being found to be "firmly fused with the anterior and posterior layers of the rectus sheath at one of the tendinous intersections" In the pathologic diagnosis he states that "the growth is macroscopically a hard fibroma, but on microscopic examination is more cellular than a hard fibroma Remains of muscle tissue are found amongst the fibres"

Jemma in 1928 reviewed the occurrence of desmoid tumors in children, but in his collected case series the majority of the tumors were not of this histogenesis In Abels's three case reports only the first patient a boy of 2 years had a tumor described microscopically as "composed of fibrous tissue slightly nucleated" This boy had a congenital tumor that remained inactive during the first year of life then grew to the size of an apple Jemma also reported a case by Sonnenschein of a female infant who at 2 months of age developed a juxtaumbilical abdominal wall tumor connected to skin which by the age of 1½ years was the size of an apple Histologic examination showed it to be composed of

* By Robert J Booher and George T Pack

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समुद्रइव गम्भीर नैव शक्य चिकित्सितम् ।
वक्तु निर विशेषेण श्लोकानामयुतैरपि ॥

—सुश्रुत संहिता

'The Science of Medicine is fathomless like the sea and can not be exhaustively narrated in thousands of couplets'

–SUSHRUT SAMHITA